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Three Essays on Hypertension Prevention and Medical Product Safety in China and the United States

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This document was submitted as a dissertation in December 2009 in partial fulfillment of the requirements of the doctoral degree in public policy analysis at the Pardee RAND Graduate School. The faculty committee that supervised and approved the dissertation consisted of Steve Garber (Chair), John Graham, and Wei Zhang.
Abstract

This dissertation addresses two important public health problems, namely hypertension prevention and medical product safety in China and the United States. The first essay employs PoPMoD, a life-table based disease model to analyze the long-term costs and effectiveness of eight selected hypertension prevention interventions in China. The results show that selected population-based interventions are more cost-effective than individual-based pharmaceutical therapies. In particular, a nationwide use of low-sodium salt substitute mandate could potentially avert 9.4 million disability-adjusted life years (DALYs) per year, resulting in an annual net savings of $3.9 billion in health expenditures.

The second essay explores the costs of medical product safety litigation in the U.S. –and thus incentives to invest in product safety - by modeling and estimating changes in the market values of pharmaceutical firms involved in ongoing medical mass torts. We model investors’ beliefs in terms of subjective probabilities and use Bayes Rule to formalize how beliefs are updated as new information becomes available. The model predicts that on average the market would respond negatively to plaintiff verdicts and positively to defendant verdicts. The model also generates six testable hypotheses regarding the relationship between the size of the market reaction and factors such as the number of earlier plaintiff (defendant) verdicts and the size of the damage award when there is an award. Our regression analysis of nine medical mass torts generates results that are largely consistent with our model predictions.

The third essay reviews recent changes and remaining problems in China’s drug safety regulation since the occurrence of several high-profile, deadly incidents during 2006-2008. While the government has made significant progress in upgrading its regulations, several important market incentive problems remain to be tackled. Among other things, substantial industry consolidation should be encouraged to close the gap between the government’s regulation capacity and the enforcement workload; pharmaceutical market incentives need to be transformed to shift the emphasis from competing on costs to competing on safety and effectiveness; a strong product liability system, which is embryonic but gaining increasing attention of policymakers’, could provide stronger private incentives not to engage in substandard pharmaceutical production and selling.
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靡不有初，鲜克有终。
--《诗经·大雅·荡》

To start well is easy; to finish well is difficult.
--Decade of Dang, Da Ya, the Book of Odes, 1000 B.C.

This dissertation has been the focus of my life in the past two years. While I am happy to be finally able to catch a glimpse of the end of the tunnel, I am even happier that I have had this opportunity to grow from a textbook reader into a policy researcher. Along this journey of ups and downs, numerous people have given me generous help, support and encouragement. Without them, I would never have made this far.

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Essay 1

Cost-Effectiveness of Individual- and Population-based Strategies to Reduce Systolic Blood Pressure in China

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1 I would like to thank the World Health Organization CHOosing Interventions that are Cost-Effective (WHO-CHOICE) project, particular Dr. Dan Chrisholm, for sharing the PoPMoD Cardiovascular model and for offering me extensive technical and data support. Dr. Bruce Neal and Dr. Nicole Li at the George Institute for International Health, Australia provided critical data input and general advice. The author is responsible for any errors or problems with this study.
Section 1: Introduction

Hypertension is one of the most important modifiable risk factors for cardiovascular disease (CVD), the leading cause of mortality both in China and worldwide [1, 2]. According to a 2000 nationally representative survey, 28.6% and 25.8% of Chinese men and women, respectively, are hypertensive [3].\(^2\) Annually, China spends more than $3 billion on hypertension treatment and $30 billion on the treatment of CVD [4, 5], representing a substantial share of its national health care resources. In the next 25 years, the financial burden of hypertension will increase even further as the number of hypertensive people is projected to grow by 65% by 2025 [6].

Given the daunting task China faces in preventing and treating hypertension, it is essential that China allocates scarce health care resources in a cost-effective way. In this paper, I use the General Cost-Effectiveness Analysis (GCEA) method, first developed by the World Health Organization CHOosing Interventions that are Cost-Effective (WHO-CHOICE) project, to analyze the long-term costs and health benefits of selected hypertension prevention interventions in China [7]. The selection of interventions took into account factors such as applicability, strength of evidence, availability of data and so forth. The effects of each intervention on individual blood pressure levels were derived from existing systematic reviews or meta-analyses. Health outcomes, quantified in terms of disability-adjusted life years (DALYs), were simulated for subpopulations differing in age and sex using PoPMoD, a life-table based longitudinal disease model that was developed by the WHO-CHOICE project [8].\(^3\)

This study seeks to improve upon existing literature on hypertension-related cost-effectiveness analysis in several important ways. First, it considers both individual- and population-based strategies, whereas most analyses to date have focused on single

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\(^2\) According to the 2005 China National Hypertension Prevention and Treatment Guideline, hypertension is defined as a systolic blood pressure of 140 mmHg or greater, or a diastolic blood pressure of 90 mmHg or greater. Throughout this paper, the term “high blood pressure” and “hypertension” are used interchangeably.

\(^3\) PoPMoD is copyrighted by the WHO. This author was permitted to use PoPMoD by the WHO. The use of the PoPMoD/MCLeague software does not imply endorsement by the WHO of any organization or any published research.
interventions. Second, in addition to estimating hypertension prevention costs, I included downstream cost savings resulting from reduced demand for CVD treatment, a cost category that has been sometimes neglected in previous studies [9]. Third, unlike many existing literature that focus exclusively on ischaemic heart disease (IHD) (ICD-9 codes 410-414) [10, 11], I considered both IHD and stroke (ICD-9 codes 430-438). This addition is important because unlike Western countries where IHD dominates, the number of patients who die from stroke is more than three times of the number that die from IHD in China [12]. Finally, I conducted an extensive set of sensitivity analyses to test the robustness of the results to varying assumptions.

Section 2 of this paper introduces and applies screening criteria that support the selection of eight interventions to reduce systolic blood pressure (SBP) in China. Section 3 describes the WHO PoPMod model and other analytical methods. Sections 4 and 5 report baseline and sensitivity analysis results. Finally, I discuss policy implications and future directions in Section 6.

Section 2: Selection of Interventions

2.1. Review of existing interventions

Two general approaches for the primary prevention of hypertension and CVD are widely recognized – individual-based interventions and population-based interventions [13]. Individual-based interventions, which seek to identify high-risk hypertensive individuals and to offer them pharmacologic treatment, have been the traditional choice for medical practitioners and policymakers [14-16]. “High-risk” individuals are usually defined as those who have a blood pressure above a certain threshold. Recently the medical community also advocates that a 10-year absolute CVD risk score, calculated through a computerized scoring system, be used to define treatment thresholds for pharmacologic treatment.

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4 IHD considered in this paper include acute-myocardial infarction, congestive heart failure and angina.
Population-based approaches focus on controlling the determinants of hypertension in the entire population. These approaches consist of mostly, but not exclusively, strategies aimed at changing population dietary intake in sodium, potassium and other nutrition elements, all of which have been linked to blood pressure levels in observational and clinical studies [17-22]. Example interventions include mass media campaigns to change diet, community-based hypertension health education, declaring of salt content in food labeling, legislation to lower the salt content of processed foods and so forth [9, 23-26].

A number of existing studies suggest that population-based hypertension prevention interventions enjoy a cost-effectiveness advantage over individual-based interventions in developed country settings [9, 13, 14]. This is because most CVD cases occur not among the small number of individuals at greatest risk, but among the much larger number of individuals at a lower level of absolute risk [10, 13]. It is unclear, however, whether the same conclusion could apply to developing countries like China, where the epidemiology of hypertension and CVD is very different from that in the West and where little evidence about the effectiveness of population-based CVD prevention interventions exists.

2.2 Selection of Interventions for China

I applied three screening criteria to select hypertension prevention interventions for China. For each intervention, I considered: (1) is there evidence that the intervention is cost-effective? (2) are there observational or clinical studies that support the effectiveness of the intervention in China? (3) does China have adequate human or technological resources to implement this strategy at a significant population coverage level?

My search resulted in two individual-based interventions: antihypertensive drug combination treatment for those have a SBP above either 140 or 160 mmHg. I excluded absolute CVD risk-based treatment because it requires a high level of computerization of the health care services and high level of risk assessment skills among physicians, neither of which is present in China [27]. In addition, the current absolute risk scoring method is based on the
Framingham Heart Study conducted in the U.S., which has been shown not applicable to the Chinese population [28].

Two population-based interventions were selected: (1) a nationwide use of low-sodium salt substitute mandate and (2) a nationwide community-based hypertension health education campaign, both of which have been demonstrated effective in China through social experiments or clinical trials. I did not consider any intervention that seeks to decrease the salt content in processed food, even though such strategies have received the greatest amount of attention in the U.S. and Europe [29-31]. A critical consideration is that unlike in Western countries where 75% of the daily sodium intake comes from processed food, 72% of daily sodium intake in Chinese diet comes from discretionary use of salt during food preparation and at the table [29, 32]. I further excluded health education through mass media, because I found little evidence about the effectiveness of such interventions in a developing country setting.

Table 1.1 summarizes all eight selected interventions. In addition to four single individual- or population-based interventions, I included all four possible combinations of these individual- and population-based interventions.

Table 1.1: Hypertension Prevention Interventions Evaluated

<table>
<thead>
<tr>
<th>Individual-based intervention</th>
<th>Population-based intervention</th>
<th>Combined individual- and population-based interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I1</td>
<td>P1</td>
<td>C1 I1+P1</td>
</tr>
<tr>
<td>I2</td>
<td>P2</td>
<td>C2 I2+P1</td>
</tr>
<tr>
<td>Antihypertensive treatment and education for SBP 140+ *</td>
<td>Nationwide use of low-sodium salt substitutes mandate</td>
<td>C3 I1+P2</td>
</tr>
<tr>
<td>Antihypertensive treatment and education for SBP 160+ #</td>
<td>Nationwide community-based hypertension health education</td>
<td>C4 I2+P2</td>
</tr>
</tbody>
</table>

* Drug treatment threshold recommended by the U.S. and Chinese National Hypertension Prevention and Treatment Guidelines [5, 15]
# Drug treatment threshold recommended by the U.K. National Hypertension Prevention and Treatment Guideline [16]
Section 3: Methods

3.1 Overview of Model Assumptions

This GCEA framework reports cost-effectiveness results in terms of the net cost effectiveness ratio ($\Delta C/\Delta E$) compared to a null scenario. The null scenario is defined as an absence of any primary hypertension prevention intervention, a key assumption differing from the more commonly-used incremental cost-effectiveness analysis framework in which the null is typically defined as the “current practice” scenario. One advantage of GCEA is that it allows researchers to evaluate not only new interventions but also the current practice itself, which is however not included in this study.

I assumed all interventions were to be implemented in a 10-year period from 2005 to 2015, although the population health effects were tracked for 100 years from 2005 to 2105. Health effects were quantified in terms of DALYs avoided. Total costs, including both hypertension prevention costs and CVD treatment costs, were first calculated for each intervention in 2005 Chinese Yuan using the Medical Component of the Chinese Consumer Price Index (CPI) [33]. They were then converted into 2005 US dollars using purchasing power parity (PPP) exchange rates [34]. All costs and health effects were discounted at a rate of 3% annually.

3.2 Estimating Health Effects

3.2.1 Intervention Effects on SBP

I1 and I2: two-drug combination treatment for those who have SBP 140 mmHg (160 mmHg) or above

Several meta-analyses of randomized clinical trials demonstrate that major classes of antihypertensive drugs, including ACE inhibitors, $\beta$-blockers, diuretics, and calcium channel blockers, lower SBP by 9-12 mmHg on average with patients with higher initial SBP achieving greater reductions [35, 36]. These drugs are also shown to reduce the total CVD
event rate, all-cause mortality, and CVD-mortality [37-42]. The efficacies of different classes of drugs are similar in size, independent and additive. Most patients will require two or more antihypertensive drugs to achieve their SBP goals. All these conclusions were shown applicable to Chinese patients in meta-analyses or systematic reviews of large-scale clinical trials conducted in China [43-45].

Following Murray et al. (2003) [9], I assumed the average SBP reduction for patients who receive treatment with two antihypertensive drugs to be one third of the difference between their initial SBP and 115 mmHg, an estimate that is consistent with above-mentioned clinical trial results. The reduction size is also proportional to patients’ adherence to the treatment. U.S.-based studies have shown that the long-term hypertensive drug adherence rate decreases from 80% in the first year to about 35% after the first two years and remains stable thereafter [46-50]. The few existing Chinese studies report similar results [51-58]. In this study I assumed the average adherence rate during the 10-year intervention period is 50%. Furthermore, because not all qualified individuals (SBP 140+ or 160+) will actually seek treatment, I further assumed a long-term treatment rate of 50% in the baseline analysis, the midway point between the 27.2% treatment rate in China in 2000 reported by the InterAsia study [3] and the 65% treatment rate in the U.S. in 2003 [59]. In the sensitivity analyses, I tested the robustness of baseline results by varying the treatment rate to a lower bound of 30% and an upper bound of 70%.

**P1:** Nationwide replacement of regular salt with low-sodium salt substitutes mandate

Low-sodium salt substitutes have been promoted as a healthy replacement of regular salt for many years [60]. Clinical trials show that replacing regular salt with low-sodium, high-potassium salt substitutes can achieve an average of 3-8 mmHg reduction in SBP among both hypertensive and normotensive individuals and significantly reduce CVD mortality [61-65]. A recent randomized, double-blind trial in rural China by the China Salt Substitute Study Collaborative Group (CSSSSCG) achieved a mean reduction of 5.4 mmHg in SBP after one-year intervention among 608 rural Chinese [66]. Because reduced sodium is replaced by
increased potassium, which also has a salty taste, clinical study participants typically cannot
detect the taste difference between regular salt and salt substitutes in blind tests [61, 63, 67].

I considered a nationwide replacement of common salt (100% sodium chloride) with the low-
sodium salt substitute used by the CSSSCG study. This salt substitute (65% sodium chloride, 25% potassium chloride, 10% magnesium sulphate) is commercially available in big grocery
stores throughout China. As clinical trials do not reflect the full health effects that salt
substitutes could achieve if used with complete adherence, as would be the case under a
national mandate, I projected the effect size of the salt substitute on SBP reduction among
individuals above age 30 based on the association between SBP and sodium intake, conditional on age, initial SBP and gender, estimated by Law et al. (1991, 1991 & 1991) (appendix A) [20-22]. Under the assumption that all discretionary use of salt will be replaced
by the salt substitute, the estimated reduction in daily sodium intake would be 26%.

The resulting reduction in SBP ranges from 1.9% to 4.7% in men and 1.6% to 4.3% in women
depending on the age group.

**P2: Nationwide community-based CVD health education campaign  similar to the Tanjin Project**

Since the early 1970s, several controlled social experiments have aimed at promoting risk-
reducing lifestyle changes through community-based CVD health education. The first such
program, the North Karelia Project in Finland, resulted in 16% and 20% net reduction in salt
intake, 4.8% and 11.3% net decreases in SBP as well as 3% and 1% net reductions in serum
cholesterol among men and women respectively after the 20-year intervention [25, 68, 69].
The Stanford Five-City Project in the U.S. achieved a 4% net reduction in SBP, a 2% net
reduction in serum cholesterol and a 13% net reduction in smoking rate among both men and
women [23]. Tianjin Project, the first major community-based CVD education project in
China resulted in a 6% net reduction in dietary salt intake, and 2.6% and 4.3% net reduction

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5 Percentage of daily sodium intake coming from discretionary use (75%) × percentage reduction in sodium intake (35%) = 26%.  

in SBP among men and women respectively. It also achieved 12% smoking rate reduction among men from 1991-1996 [32, 70, 71].

The current study considered a nationwide community-based CVD health education program assumed to have health effects similar to those of the Tianjin Project. In the baseline analysis, I included only net health benefits resulted from SBP reduction. I explored how the smoking reduction component of the program affects the cost-effectiveness ratio in the sensitivity analyses.

Table 1.2 summarizes the assumed health effects of all four single interventions (I1, I2, P1, and P2). For the combination interventions (C1-C4), the effects of population-based interventions (P1 or P2) were applied first. Individuals remaining above the drug treatment thresholds (140 or 160 mmHg) were then subject to the same health effects as those with I1 or I2.

**Table 1.2: Health Effects of Interventions Evaluated**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reduction in SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>I1 &amp; I2</td>
<td>33% × (original SBP - 115 mmHg)</td>
</tr>
<tr>
<td>P1*</td>
<td>1.9%-4.7% in men depending on age group 1.6%-4.3% in women depending on age group</td>
</tr>
<tr>
<td>P2</td>
<td>2.6% reduction in SBP among men 4.3% reduction in SBP among women</td>
</tr>
</tbody>
</table>

* The age groups are 30-44, 45-59, 60-69, 70-79, 80 and above.

### 3.2.2 Effects on CVD and Survival

**Evidence from Clinical Trials**

Overviews of randomized controlled trials have confirmed the reduction of CVD risks with blood pressure lowering [72-76]. These studies suggest that a 10 mmHg lower SBP is on average associated with a 30-40% lower risk of stroke and a 20-25% lower risk of CVD. Recent meta-analyses of large scale Chinese antihypertensive clinical trials report similar results for the Chinese population [37, 43-45]. The reductions are similar for those with or without hypertension and for both females and males.
The PoPMoD CVD Model

In the present study, the effects of hypertension prevention interventions on population SBP levels were translated into effects on CVD and survival using the PoPMoD model. This computer-based multi-state dynamic life table model, as described in detail elsewhere [8], forecasts CVD incidence, prevalence and mortality under various assumptions regarding risk factor levels and treatment effects.

As depicted in Figure 1.1, PoPMoD simulates population evolution by age and by sex subject to births, deaths and two CVD conditions, i.e. IHD and stroke. The model population is divided into six age groups: below 30, 30-44, 45-59, 60-69, 70-79 and 80 and above. Each year a new birth cohort enters the model, some people develop either IHD or stroke or both conditions, and some people exit the model by death, either due to CVD conditions or other non-CVD mortality risks. The transitions of members from one state to another are governed by a system of ordinary differential equations reflecting the population CVD epidemiological parameters (incidence rates, prevalence rates, remission rates and case-fatalities), which are in turn determined by the distributions of CVD risk factors (SBP ≥ 140 mmHg, total cholesterol ≥ 5.7 mmol/L, body mass index (BMI) ≥ 28 kg/m² and smoking) in the population.

Baseline year (2005) Chinese population by age and sex were obtained from the 2005 United Nations Population Division projection [77]. Age- and gender-specific live births and mortality rates projected for 2005-2050 were obtained from the same source and assumed to remain the same for the period of 2051-2105. I estimated baseline distributions of SBP, total cholesterol, and smoking rate by age and gender using published data from the 2000 InterAsia Study [78-81]. Baseline age- and gender-specific distributions of BMI were obtained from the Asia-Pacific Cohort Studies Collaboration (APCSC) database [82, 83]. Baseline age- and gender-specific CVD epidemiological parameters were approximated by the West-Pacific Region B1 (WPR-B) data from the Global Burden of Disease 2000 (GBD2000) study [85]. 6 (A complete list of all data inputs and sources is included in Appendix C)

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6 Chinese population accounts for more than 90% of the total population in the WPR-B region.
I calibrated all original epidemiological parameters with a special tool DisMoD II, also developed by the WHO-CHOICE, to ensure internal consistencies [86]. Within subpopulations defined by age and gender, each individual’s risk profile was randomly simulated based on the mean value and standard deviation of each risk factor for that subgroup.

I implemented a two-step adjustment process to construct the GCEA null scenario. First, I adjusted age- and gender-specific SBP distributions and CVD incidence rates by eliminating the impacts of existing hypertension prevention interventions in China, using information about the current population coverage of these interventions from the InterAsia study [3, 87, 88]. Next I adjusted CVD case-fatality rates by eliminating the impact of existing hospital-based CVD treatment interventions based on hospital-based treatment coverage information collected by the WHO-MONICA project, GBD 2000, and the Clinical Pathway for Acute Coronary Syndromes in China (CPACS) project [87-90]. The effect sizes of both existing hypertension prevention and CVD treatment interventions were derived from existing meta-analyses. Out-of-hospital case-fatalities were assumed to be unaffected.

Source: Lauer et al., WHO (2003) [8]
Once I had the null scenario SBP distributions, I applied the health effects of each of the eight selected hypertension prevention interventions (I1-C4) by adjusting the mean SBP level for each age- and gender-specific subgroup. The PoPMoD assumes the effect of SBP reduction on CVD mortality was mediated by its impact on individuals’ relative risks of IHD and stroke, assuming all other CVD risk factors consistent with or without interventions. Each individual’s relative risk of IHD and stroke events for a unit change in SBP, cholesterol, BMI and smoking, conditional on one’s age and gender, was projected using multiple logistic risk functions estimated by the WHO [9, 91].

To project the full effect of SBP reduction on CVD mortality and DALYs, I used a CVD disease model that simulates the disease progression after one experiences a specific type of CVD event (Figure 1.2). For IHD events, I considered the first-ever acute-myocardial infarction (AMI) subdivided into those that is fatal in the first 28 days and those that survive the first 28 days, angina subsequent to AMI, and congestive heart failure (CHF) subsequent to AMI. For stroke events, I consider the first-ever ischemic stroke that is fatal and nonfatal in the first 28 days and the first-ever non-ischemic stroke that is fatal and nonfatal in the first 28 days. Because the case-fatilities of both AMI and stroke is substantially higher in the first 28 days, I modeled events fatal within the first 28 days via the background mortality rate. A higher relative risk (RR) of stroke was incorporated for those with previous AMI and a higher RR for AMI for those with previous stroke.
Figure 1.2: The CVD Disease Model

No CVD events
1 - IX(a) - IC(b)

First-ever AMI
IX(a)

First-ever Stroke
IX(c)

Survive to next age group
1 - m1

Die due to non-CVD causes
m1

Die in 28 days
m2

Survive in 28 days
IX1

Die for a recurrent AMI
f(ami)

Die for CHF
f(chf)

Survive to next age group
1 - f(ami) - f(chf) - IC2

Develop a stroke (move to stroke branch)
IC2

Die in 28 days
m3

Die for a recurrent stroke
fc

Survive in 28 days
IC1

Survive to next age group
1 - fc - IX2

Develop AMI (move to AMI branch)
IX2

Links to Figure 1:

a. background mortality \( m = m1 + m2 + m3 \)
b. case-fatality rate in X, \( fx = f(ami) + f(chf) \)
c. case-fatality rate in X, \( fc \) is not shown in this graph
d. all remission rates, \( RX1, RX2, RC1, RC2 \) are assumed to be 0
3.2.3 Effects on DALYs

Population health outcomes were quantified in terms of DALYs by tracking what happens to each age and gender group of the population over 100 years with each intervention compared to the null scenario. First developed by the GBD 2000 study, DALY is a summary measure of population health that combines in a single indicator years of life lost from premature death and years of life lived with disabilities. DALYs have become increasingly used in the cost-effectiveness literature [9, 92-97]. Mathematically, DALYs were calculated by multiplying the number of years lived with a disease condition by the disability weight for that condition. For individuals that have multiple disease conditions, DALYs are the number of years lived with those conditions times the joint disability weight for those conditions. A detailed discussion of the principles and techniques of DALY can be found in Murray & Lopez (1996) [98]. In this study I used the disability weights for living with CVD conditions estimated by the West Pacific Region from the GBD 2000 study [99] (see appendix C).

3.3 Estimating Costs

3.3.1 Overview of Cost Structure

For each intervention, the total costs included prevention costs associated with implementing that intervention and subsequent cost savings resulting from reduced demand for CVD treatment. I did not consider the costs of productivity loss associated with CVD because little data exist regarding the employment and income levels of Chinese people aged 50 or above, arguable the most relevant age groups for CVD. Similarly, I did not include the costs of treating any non-CVD illness during the added years of life that would not have occurred in the absence of treatment because I found little data about the age- and gender- specific non-CVD-related medical expenditure among Chinese people. In theory, these two categories of omitted costs should affect the total costs in opposite directions, although I did not find any reliable evidence to determine whether the costs of productivity loss are larger or smaller than the costs of treating non-CVD illnesses during the added life years. Depending on the relative
size of each of these two types of cost, the total costs calculated in this study would tend to over or underestimate the full social costs of each intervention.

Quantities of patient-level resource inputs required for each individual-based intervention (e.g. frequency of outpatient visits, medication dosage, lab tests) were identified from the Chinese National Clinical Guideline for Hypertension [5, 15], assuming Chinese physicians treat hypertensive patients consistent with what the Guideline recommends.

For combination interventions (C1-C4), the costs of population-based interventions were first applied. Costs of individual-based interventions (I1 or I2) were then applied to individuals projected to remain above the individual-based treatment thresholds.

3.3.2 Prevention Costs

For each of the two individual-based interventions, the prevention costs included the costs associated with individuals seeking primary-care (such as office visits, diagnostic lab tests and medicine) for controlling their hypertension. I did not include any possible costs associated with changing the current recommended hypertension pharmacologic treatment threshold or educating health care providers about this change because I expect such activities could be accommodated by the health care system’s routine operations and thus would involve little or no incremental costs. The prevention costs of nationwide use of low-sodium salt substitute mandate consisted of the incremental cost difference between the regular salt and the salt substitute. The prevention costs of the community-based CVD education were based on published estimates for the Tianjin Project [100]. Table 1.3 at the end of this section summarizes prevention costs for each of the selected interventions.

It should be noted that both medical services prices and drug prices are regulated in China. Medical services prices, in particular, are capped at very low levels and therefore do not reflect the true social costs of providing these services. On the other hand, it is well known that Chinese physicians and hospitals cross subsidize basic services with a 15%-45% markup they are allowed to charge on drugs [102, 103]. In other words, while the regulated medical
services prices are likely to be lower than the social costs of these services, retail drug prices are likely to be higher than the social costs. Because I did not find any reliable way to estimate the respective true social costs of medical services and drugs, I relied on government retail price caps for both medical services and drugs in the baseline analysis, assuming the combined prices of medical services and drugs reflect reasonably accurately their true combined social costs. I explored the impact of different assumptions on medical costs in the sensitivity analyses.

Office visits
In China, prices for medical services are regulated by the provincial or metropolitan Development and Reform Commissions (DRCs). In this study, I used Beijing DRC’s 2000 price standard (1.5 Yuan per visit) as my primary source for the cost of office visit [104]. I further assumed that each patient who was taking the antihypertensive drug treatment would make two office visits per year. The annual office visit cost per person would be 3 Yuan (4 in 2005 Yuan or $1.2 in 2005 U.S. dollar).

Laboratory tests
The costs of laboratory tests for hypertensive patients were also estimated using the Beijing DRC standards [104]. For lab tests, I considered electrocardiogram (8 Yuan), urinalysis (8 Yuan), blood glucose and hematocrit (21Yuan), serum potassium (4 Yuan), creatinine and calcium (12Yuan); and a lipid profile (30 Yuan), all of which were recommended by the National Guideline [5]. I further assumed that each patient would take the lab tests 1.5 times per year. Thus the annual cost for lab tests per patient was 124.5 in 2000 Yuan (or 127.2 in 2005 Yuan or $36.9 in 2005 U.S. dollar).

Antihypertensive medication costs
I estimated antihypertensive medication costs using the 2007 National Development and Reform Committee’s (NDRC) Upper Limit Retail Prices Index [105] and deflated them to 2005 price levels with the medical component of the CPI. To estimate the average price of a two-drug combination with any two classes of the major antihypertensive drugs, I first identified the median prices of each of the four major classes of antihypertensive drugs (ACE
inhibitors, β - blockers, diuretics and calcium channel blockers). Next I computed the average daily price of the six possible two-drug combinations for the standard dosages. This resulted 2.5 Yuan per person per day or 927 Yuan per person per year in 2007 (or 900 in 2005 Yuan or $260.9 in 2005 U.S. dollar), This result is similar to the annual medication costs for hypertensive patients reported by an outpatient survey conducted in Beijing [106].

Salt substitute
The cost of the salt substitute was obtained from the retail price of the salt substitute used in the CSSSCG study. The retail price of this salt substitute is approximately 3.4 Yuan/kg [107], or roughly 50% more expensive than the regular salt sold in China. Under the assumption that each person consumes 12g of salt substitute per day, the annual incremental per person cost for the salt substitute is 4.9 Yuan in 2005 or ($1.4 in 2005 U.S. dollars).

Community-based CVD education
The average per person cost of the Tianjin Project was 36.2 Yuan in 2005 or $10.5 in 2005 U.S. dollar [100]. Estimated using the ingredient-based approach described in the WHO-CHOICE project, this number includes the costs of developing educational materials, personnel costs, transportation costs, utility costs, equipment costs and other related medical services costs. If there are substantial economies of scale in these activities—due, for example, to fixed costs of equipment or developing educational materials—then my use of average costs from the relatively small Tianjin Project would tend to overstate the true average costs of a nationwide intervention.

Table 1.3: Prevention Costs Assumed in Baseline Analysis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost category</th>
<th>Quantity per year per person</th>
<th>Cost per year per person 2005 Yuan (SPPP 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I1 &amp; I2</td>
<td>· Medication</td>
<td>· Standard doses</td>
<td>1.5 times</td>
</tr>
<tr>
<td></td>
<td>· Outpatient visits</td>
<td></td>
<td>1.5 times</td>
</tr>
<tr>
<td></td>
<td>· Lab tests</td>
<td></td>
<td>1.5 times</td>
</tr>
<tr>
<td>P1</td>
<td>· Salt substitutes</td>
<td>· 4.4 kg</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>· Program costs</td>
<td>N.A.</td>
<td></td>
</tr>
</tbody>
</table>
3.3.3 Costs of Treating CVD

Acute hospitalization costs for AMI, CHF, ischemic stroke and non-ischemic stroke

Acute hospitalization costs for CVD events were obtained from the China Health Statistics Yearbook 2008 (Table 1.4) [99]. For patients who died in the hospital, I assumed they incurred 70% of the hospital costs that one who survived would incur.

Table 1.4: Acute Hospitalization Costs for CVD

<table>
<thead>
<tr>
<th>CVD event</th>
<th>Bed cost per day (Y)</th>
<th>Medication cost (Y)</th>
<th>Treatment cost (Y)</th>
<th>Average hospital stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>351</td>
<td>3,649</td>
<td>3,463</td>
<td>10.8</td>
</tr>
<tr>
<td>CHF</td>
<td>261</td>
<td>2,109</td>
<td>802</td>
<td>11.4</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>339</td>
<td>3,546</td>
<td>939</td>
<td>12.8</td>
</tr>
<tr>
<td>Non-ischemic stroke</td>
<td>399</td>
<td>4,255</td>
<td>1,621</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Source: China Health Statistics Yearbook 2008

Acute hospitalization costs for angina

There are no available data regarding the hospitalization cost for angina in China. Stinnett et al. (1996) estimates that the average hospitalization cost for angina is roughly 40% of that of CHF in the U.S. [108] Assuming the same proportion applies to China, the average hospital cost for angina would be 1,633 per stay in 2005 Yuan (or $473 in 2005 U.S. dollar). I further assumed that half of the patients with new-onset angina were hospitalized.

Annual hospitalization costs for AMI and stroke

The OASIS study reports that the first two-year re-hospitalization rate for Chinese patients who survived the first 28 days after an AMI is 33.3% [109]. Assuming the costs for AMI hospitalization are the same as those for the initial hospitalization, the average annual re-hospitalization costs for AMI patients in the first two years would be 1,934 in 2005 Yuan (or $561 in 2005 U.S. dollar). Based on a U.S. study [110], I further assumed that the annual hospitalization costs for all subsequent years were 46% of those of the first two years, i.e. 889 in 2005 Yuan (or $258 in 2005 U.S. dollar).

To estimate the first-year hospitalization costs for the first-ever stroke survivors, I multiplied the probability of a stroke recurrence in the first year by the hospitalization costs for a stroke
in the first 28 days, assuming the hospitalization costs for recurrent stroke were the same as those for the initial stroke. A review of existing literature shows that the recurrent rates of ischemic and non-ischemic strokes in the first two years among Chinese patients are 11% and 24.3% respectively [12, 111]. The resulting annual hospitalization costs for the first two years were 11% $5,990 = 719 Yuan ($208.4 in 2005 U.S. dollar) for ischemic stroke and 24.3% $8,491 = 2,063 Yuan ($598.0 in 2005 U.S. dollar) for non-ischemic stroke. For all subsequent years, the annual hospitalization costs were projected to be 3% of the initial 28 days [112], resulting in an annual cost of 180 Yuan ($52.2 in 2005 U.S. dollar) for ischemic stroke or 254 Yuan ($73.5 in 2005 U.S. dollar) for non-ischemic stroke.

**Annual outpatient costs and medication costs for AMI and stroke survivors**

Chinese National Health Statistical Center reported in 1998 that the average outpatient costs (including medication cost) per visit after the first AMI were 238 Yuan and 213 Yuan for stroke [113]. In addition, a survey conducted in 1998 in Tianjin suggests that on average 28-day AMI survivors paid for 4.92 Yuan per outpatient visit [114]. Another survey conducted in Beijing reports that the average per outpatient visit for stroke survivors was 7.7 Yuan [115]. Assuming both IHD and stroke survivors make an average of five outpatient visits per year, the annual outpatient costs would be 1,190 Yuan for MAI survivors and 1,065 Yuan for stroke survivors in 1998 (or $345 and $308 in 2005 U.S. dollar).

**Section 4: Results**

Table 1.5 summarizes the total annual costs, annual health effects in terms of DALYs averted, and cost-effectiveness ratio for each of the eight selected interventions. Generally speaking, the smaller the cost-effective ratio is, the more cost-effective one intervention is. A negative sign of the cost-effective ratio indicates that the intervention would result in net savings in health care expenditure. The WHO recommends that an intervention be considered “cost-effective” if it has a cost-effectiveness ratio less than three times of a country’s GDP per capita and “highly cost-effective” if the cost-effectiveness ratio is less than the GDP per capita [116]. By these standard, all eight selected interventions are highly cost-effective as
their cost-effectiveness ratios are far less than China’s GDP per Capita, which was $4,091 in 2005 [98].

Nationwide use of low-sodium salt substitute mandate (P1) is the most cost-effective intervention, resulting in net annual savings of $424 per DALY averted. The two combination interventions that involve nationwide use of salt substitutes (C1 and C2) would also lead to net annual savings in health. Individual-based antihypertensive combination drug treatment for SBP 160+ (I2) is more cost-effective than antihypertensive treatment for SBP 140+ (I1). Overall, the two antihypertensive drug treatment interventions (I1 and I2) have the smallest total amount of health benefit (DALYs averted per year) and the four combined interventions (C1-C4) have the largest total health benefits.

Table 1. Annual costs, effects and cost-effectiveness of interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Prevention Costs ($×10^6)</th>
<th>CVD Treatment Savings* ($×10^5)</th>
<th>Total Costs ($×10^5)</th>
<th>DALYS averted</th>
<th>Cost/DALY ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual-based</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I1 (drug treatment for SBP 140+)</td>
<td>9,349</td>
<td>-4,234</td>
<td>5,115</td>
<td>8,165</td>
<td>626.5</td>
</tr>
<tr>
<td>I2 (drug treatment for SBP 160+)</td>
<td>4,175</td>
<td>-4,054</td>
<td>122</td>
<td>7,716</td>
<td>15.8</td>
</tr>
<tr>
<td>Population-based</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1 (salt substitute mandate)</td>
<td>759</td>
<td>-4,679</td>
<td>-3,999</td>
<td>9,430</td>
<td>-424.1</td>
</tr>
<tr>
<td>P2 (community CVD education)</td>
<td>5,705</td>
<td>-5,208</td>
<td>496</td>
<td>9,768</td>
<td>50.8</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1 (I1+P1)</td>
<td>7,698</td>
<td>-7,898</td>
<td>-200</td>
<td>15,291</td>
<td>-13.1</td>
</tr>
<tr>
<td>C2 (I1+P2)</td>
<td>3,786</td>
<td>-7,729</td>
<td>-3,943</td>
<td>14,898</td>
<td>-264.7</td>
</tr>
<tr>
<td>C3 (I2+P1)</td>
<td>12,620</td>
<td>-8,219</td>
<td>4,401</td>
<td>15,588</td>
<td>282.3</td>
</tr>
<tr>
<td>C4 (I2+P2)</td>
<td>9,009</td>
<td>-8,058</td>
<td>951</td>
<td>15,223</td>
<td>62.5</td>
</tr>
</tbody>
</table>

* Annual costs for CVD treatment under the null scenario is 83,147 ($×10^6)

The cost-effectiveness ratios alone do not tell the whole story. Nationwide use of salt substitutes (P1) has the most favorable cost-effectiveness ratio, but it does not result in the largest number of DALYs averted. From a policy perspective, the best intervention is the one that achieves the greatest health benefits for a given budget. The best policy option for one budget level may or may not be the best option for a different budget level. To identify the expansion path of the optimal policy choice as the total budget grows, I calculated the incremental costs and benefits of each intervention compared with the next best option for various budget levels. In this chart, the X axis indicates the total number of DALYs averted and the Y axis represents the total amount of resources required. The slope of the line connecting the origin to each point is thus the net cost-effectiveness ratio of that intervention.
The blue line in Figure 1.3, i.e. the expansion path, demonstrates in which order interventions would be adopted as the total amount of available resources increases. When budget is very low, P1 will be adopted first. As the total budget increases to nearly $4,000 million per year, C2 becomes a better policy as it achieves a higher level total health benefit than P1 does and it has the best cost-effectiveness ratio among all remaining alternatives. Similarly, when the total budget increases to near $8,000 million per year, C1 replaces C2 as the best policy option.

Figure 1.3: Expansion Path of Hypertension Prevention Interventions

Section 5: Sensitivity Analyses

Delay in health effects
Clinical trials have noted a delay between SBP reduction and changes in CVD health outcomes [72-75]. The WHO Comparative Risk Assessment study recommends a three-year risk reversal window on the basis of a systematic review of the time taken for risk reversal after a sustained reduction in SBP from both observational and clinical studies [117]. Assuming interventions implemented in 2005 would begin having an effect on CVD incidence rates only in 2008, the cost-effectiveness ratios for each of the eight interventions increased, i.e. becoming less cost-effective, but the relative ranking of all interventions
remained the same. Furthermore, all eight interventions remained in the “highly cost effective” category by the aforementioned WHO cost-effective standards.

**Antihypertensive drug treatment rate**

Two separate analyses assessed the impact of lowering the hypertension treatment rate to 30%, a lower bound based on the 2000 InterAsia survey [78] and to 70%, an upper bound equal to the 2003 U.S. hypertension treatment rate [59]. As the treatment rate increases, both the total health benefits and the total costs increase, but the health benefits grow faster than the total costs. As a result, the cost-effectiveness of both individual-based interventions (I1 and I2) improves with a higher treatment rate. Nevertheless, the relative rankings of both interventions did not change when the treatment rate changed from 30% to 70%.

**Costs of salt substitutes**

The cost-effectiveness ratio of nationwide use of salt substitutes (P1) would remain negative, i.e. net savings in health expenditure, as long as the cost of the salt substitutes does not exceed $2.0/kg, or an increase by 624% from its current price. This is because the annual cost savings in CVD treatment ($3.6 per person) far exceeds the annual prevention costs ($0.5 per person) associated with this intervention.

**Costs of CVD treatment**

Two separate analyses assessed the impact of changes in the assumed CVD treatment costs. A 15% decrease in the CVD treatment cost would simultaneously increase the cost-effectiveness ratios of all interventions, i.e. less cost-effective because of reduction in treatment costs involve less projected cost savings. A 15% increase in the CVD treatment, on the other hand, would simultaneously decrease the cost-effectiveness ratios of all interventions. In either case, however, the relative rankings of the eight interventions did not change (Figure 1.4).
Health effects of community-based CVD health education

In the baseline analysis, I considered the health effects only in terms of net reduction in SBP for the nationwide community-based CVD health education program (P2). If I took into account the benefit of smoking reduction associated with this program as the Tianjin Project has demonstrated, the cost-effectiveness ratio of P2 improved from $50.8 per DALY averted to a negative $-24 per DALY averted, i.e. resulting in net savings of health expenditure. Similar, the cost-effectiveness ratios of the two combined interventions that involved P2, i.e. C3 and C4, also improved from $282.3 to $216.2 and from $62.5 to $14.6 respectively. Table 1.6 and Figure 1.5 report the new cost-effectiveness results when the smoking reduction benefit of P2 was included.

Table 1.6: Annual costs, effects and cost-effectiveness when smoking reduction benefit included

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Prevention Costs ($×10^6)</th>
<th>CVD Treatment Savings* ($×10^6)</th>
<th>Total Costs ($×10^6)</th>
<th>DALYs ($×10^2)</th>
<th>Cost/DALY ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual-based</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I1 (drug treatment for SBP 140+)</td>
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</tr>
<tr>
<td>Population-based</td>
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</tr>
<tr>
<td>P1 (salt substitute mandate)</td>
<td>759</td>
<td>-4,579</td>
<td>-3,999</td>
<td>9,430</td>
<td>-424.1</td>
</tr>
<tr>
<td>P2 (community CVD education)</td>
<td>5,705</td>
<td>-5,980</td>
<td>-276</td>
<td>11,500</td>
<td>-24.0</td>
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<tr>
<td>Combined</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C1 (I1+P1)</td>
<td>7,698</td>
<td>-7,898</td>
<td>-200</td>
<td>15,291</td>
<td>-13.1</td>
</tr>
<tr>
<td>C2 (I1+P2)</td>
<td>3,786</td>
<td>-7,729</td>
<td>-3,943</td>
<td>14,898</td>
<td>-264.7</td>
</tr>
<tr>
<td>C3 (I2+P1)</td>
<td>12,620</td>
<td>-8,894</td>
<td>3,726</td>
<td>17,231</td>
<td>216.2</td>
</tr>
<tr>
<td>C4 (I2+P2)</td>
<td>9,009</td>
<td>-8,762</td>
<td>247</td>
<td>16,874</td>
<td>14.6</td>
</tr>
</tbody>
</table>
Section 6: Discussion

Among all eight individual- and population-based interventions, nationwide use of salt substitutes by legislation is most cost-effective in China. This result is robust under different model assumptions and consistent with the result from an earlier study by Murray et al. that examined different hypertension prevention interventions at the global and regional levels (2003) [9]. The beneficial effects of sodium intake reduction have been well-recognized in the international public health communities [5, 15, 29, 31]. Wide use of low-sodium salt substitutes, however, has so far been promoted only in a few European countries, particularly in Finland [60]. A recent study by Pietinen et al. (1996) suggests that decreased dietary sodium intake might be responsible for a substantial reduction in CVD deaths in Finland during 1972-1992 [68]. In the United States, low-sodium salt substitutes are sold as an over-the-counter product in pharmacies and grocery stores for hypertensive patients, although salt substitutes have not received as much attention from public health advocates as they do in Europe.

China offers a very promising environment for large-scale use of low-sodium salt substitutes. Chinese people on average consume more than 12g of salt everyday, , the highest among all
countries included in the INTERMAP study, far exceeding the 5g per day standard recommended by the WHO [117, 118]. With more than 72% of dietary salt intake comes from home cooking and discretionary use at table instead of from processed food [29, 32], replacing regular salt with low-sodium salt substitutes is a very promising solution to reduce population dietary sodium intake [119]. From a policy implementation point of view, China has historically been an excellent example of using salt fortification to improve population health. In particular, China launched nationwide mandatory replacement of regular salt with iodized salt in the early 1990s. As a result, the average iodine deficiency rate for children age 8-10 has fallen from 20.4% in 1995 to 8.8% in 1999 [120]. China is also the only country to add medication diethycarbamazine in dietary salt, which has helped to essentially eliminate lymphatic filariasis, a mosquito-transmitted disease that is ranked as the second leading cause of disability worldwide in China [121, 122].

Several issues regarding the low-sodium salt substitutes that are not accounted for in the current study deserve further consideration. First, the potential interaction between salt substitutes and antihypertensive drugs needs to be further studied. Existing clinical trials have not found salt substitutes interfere with the efficacies of major antihypertensive drugs, although rare cases of hyperkalaemia have been reported among patients who have severe renal disease and are simultaneously taking potassium-sparing antihypertensive drugs [123]. Second, despite clinical trials have shown that a moderate and repeated reduction of sodium and increase of potassium do not produce discernable taste differences, it is generally understood that the higher the potassium content is, the bitter a salt substitute tastes [67]. Future research should study more about the optimal mix of sodium, potassium and other mineral components to achieve the best balance of efficacy, taste and safety. Before the above mentioned issues are well-studied and understood, population-wide replacement of regular salt with low-sodium salt substitutes should be implemented sequentially, starting with low renal disease risk populations and low-risk communities before gradually expanding to the entire population.

7 Continued availability of regular salt during such a transition period raises the possibility that low-risk individuals (who are supposed to use the salt substitute) will attempt to continue to use regular salt, which will remain available to those with high risk of renal disease. Thus, there may be enforcement efforts and additional costs to such a sequential policy approach.
Community-based CVD health education program is not as cost-effective as treating individuals with SBP 160 + with antihypertensive drugs in the baseline analysis. This result was reversed after taking into account community-education’s impact on male smoking rate. When reductions in multiple CVD risk factors were considered, nationwide community-based CVD health education resulted in the largest total amount of health benefits and is more cost-effective than individual-based drug treatment interventions. It is worth noting that China’s Tianjin project, which was the basis of the current study, achieved lower reductions in SBP and in smoking rate than similar programs conducted outside China. For example, both the North Karelia project in Finland and the Stanford Five-City project achieved significantly higher reductions in population SBP and in population smoking [25, 68, 69, 124]. If future Chinese community-based CVD health education programs could improve their effectiveness to a level similar to that of the North Karelia project or the Stanford Five-City project, even greater amount of total health benefits and better cost-effectiveness ratios could be achieved at the population level.

Individual-based antihypertensive drug treatment achieves a more favorable cost-effectiveness ratio when the treatment threshold is 160 mmHg rather than 140 mmHg and when the treatment rate is higher. Currently only 27.2% of Chinese hypertensive individuals are taking antihypertensive drugs [78]. The decisions to initiate and to adhere to antihypertensive drug treatment are largely private choices made by individuals themselves. However, public policy can influence such decisions by improving the access to antihypertensive drugs, increasing the general awareness of hypertension and people’s knowledge about the health risks of sustained high blood pressure. In the near future, policymaker can improve the overall cost-effectiveness of drug treatment by changing the treatment threshold from the current level of 140 mmHg to 160 mmHg. In the long run, public policy should be designed towards expanding health insurance coverage among urban poor and among rural population, and towards increasing the coverage of blood pressure screening.

The current study has several limitations. First, it examines only the aggregate costs and benefits associated with each selected intervention. As it is often the case for health
interventions, one intervention might have very different impacts on men and women, young people and the elderly, low-risk groups and high-risk groups. Future study should further look into each of these subpopulations to offer policy recommendations that are tailored to the needs of different population groups. Second, for individual-based drug treatment interventions, prevention costs were estimated based on prices as regulated by the Chinese central or provincial governments. Arguably these prices do not reflect the true social costs of health care services that are performed by public hospitals or health clinics. Future studies could potentially improve the cost estimates by incorporating government subsidies devoted for hypertension prevention and CVD treatment.

References:


40. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. *JAMA,* 2002, 288: pp. 2981-2997.


50. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic. *JAMA*, 2002, 288: pp. 2981-2997.


105. Liu, Y., Personal communication with Dr. Bruce Neal and Dr. Nicole Li in August, 2008.


Appendix A: predicted change in systolic blood pressure by gender and age group after nationwide use of a low-sodium salt substitute by legislation

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-44</td>
<td>-1.9%</td>
<td>-1.6%</td>
</tr>
<tr>
<td>45-59</td>
<td>-2.4%</td>
<td>-2.1%</td>
</tr>
<tr>
<td>60-69</td>
<td>-3.2%</td>
<td>-3.0%</td>
</tr>
<tr>
<td>70-79</td>
<td>-3.9%</td>
<td>-3.6%</td>
</tr>
<tr>
<td>80+</td>
<td>-4.7%</td>
<td>-4.3%</td>
</tr>
</tbody>
</table>

* Assume the content of the salt substitute is 65% sodium, 25% potassium and 10% magnesium

** Assuming all discretionary use of salt is replace by the salt substitute, i.e. daily sodium intake reduction is 35%×75%=26%

Estimating method based on:


Lawes C, Feigin V, Rodgers A. *Estimating reductions in blood pressure following reductions in salt intake by age, sex and WHO region.* Auckland: ClinicalTrials Research Unit, University of Auckland, 2002.
### Appendix B: Key Model Parameters for the PoPMoD Simulation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Source(s)</th>
</tr>
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<tbody>
<tr>
<td><strong>Demography</strong></td>
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</tr>
<tr>
<td>Live birth</td>
<td>UNPD 2005 projection [1]</td>
</tr>
<tr>
<td>Population by age and by gender</td>
<td></td>
</tr>
<tr>
<td>Mortality rates by age and by gender</td>
<td></td>
</tr>
<tr>
<td><strong>Epidemiological parameters for IHD</strong></td>
<td></td>
</tr>
<tr>
<td>Incidence of AMI by age and by gender</td>
<td>WHO-MONICA Beijing [2]</td>
</tr>
<tr>
<td>Mortality rates by age and by gender</td>
<td>Global Burden of Disease 2000 [3, 4]</td>
</tr>
<tr>
<td>24-hour case fatality for AMI</td>
<td></td>
</tr>
<tr>
<td>28-day case fatality for AMI</td>
<td></td>
</tr>
<tr>
<td>Out-of-hospital case fatality for AMI</td>
<td></td>
</tr>
<tr>
<td>Incidence of long-term AMI survivors</td>
<td></td>
</tr>
<tr>
<td>Prevalence of long-term AMI survivors</td>
<td></td>
</tr>
<tr>
<td>Case fatality for long-term AMI survivors</td>
<td></td>
</tr>
<tr>
<td>Mortality for AMI</td>
<td></td>
</tr>
<tr>
<td>Incidence for angina pectoris</td>
<td></td>
</tr>
<tr>
<td>Prevalence for angina pectoris</td>
<td></td>
</tr>
<tr>
<td>% of AMI survivors that develop CHF</td>
<td></td>
</tr>
<tr>
<td>Incidence of congestive heart failure (CHF)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of CHF</td>
<td></td>
</tr>
<tr>
<td>Case fatality of CHF</td>
<td></td>
</tr>
<tr>
<td><strong>Epidemiological parameters for stroke</strong></td>
<td></td>
</tr>
<tr>
<td>Incidence for first-ever stroke</td>
<td>WHO-MONICA Beijing [2]</td>
</tr>
<tr>
<td>28-day case fatality for stroke</td>
<td></td>
</tr>
<tr>
<td>% of 28-day fatal stroke cases that are out-of-hospital</td>
<td></td>
</tr>
<tr>
<td>% of 28-day fatal stroke cases that are ischaemic stroke</td>
<td></td>
</tr>
<tr>
<td>Incidence of long-term stroke survivors</td>
<td></td>
</tr>
<tr>
<td>Prevalence of long-term stroke survivors</td>
<td></td>
</tr>
<tr>
<td>Case fatality for long-term stroke survivors</td>
<td></td>
</tr>
<tr>
<td>% for long-term stroke survivors dying from stroke</td>
<td></td>
</tr>
<tr>
<td>Mortality for stroke</td>
<td></td>
</tr>
<tr>
<td><strong>Current coverage of interventions</strong></td>
<td></td>
</tr>
<tr>
<td>For AMI during acute phase (28 days)</td>
<td>WHO-MONICA Beijing [2]</td>
</tr>
<tr>
<td>For AMI during post-acute phase</td>
<td>Global Burden of Disease 2000 [3, 4]</td>
</tr>
<tr>
<td>For stroke during acute phase (28 days)</td>
<td>CPACS [5, 6]</td>
</tr>
<tr>
<td>For stroke during post-acute phase</td>
<td></td>
</tr>
<tr>
<td>For CHF</td>
<td></td>
</tr>
</tbody>
</table>

Appendix C: Disability Weights Used for Estimating of DALY

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Disability Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>0.44321</td>
</tr>
<tr>
<td>Angina</td>
<td>0.16109</td>
</tr>
<tr>
<td>CHF</td>
<td>0.24683</td>
</tr>
<tr>
<td>Acute stroke</td>
<td>0.92000</td>
</tr>
<tr>
<td>Long-term Stroke Survivor</td>
<td>0.24309</td>
</tr>
</tbody>
</table>

Essay 2

Confronting Heterogeneity in Litigation Event Studies—the Case of Trial Verdicts in Medical Products Mass Torts

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8 To be submitted to an academic journal with Steve Garber as a co-author.
Section 1: Introduction

Many prominent mass torts in the U.S. have involved medical products (i.e., pharmaceuticals and medical devices). During the past three decades, mass torts involving products such as silicone-gel breast implants, Fen-phen and Vioxx, have cost defendants billions of dollars in defense and indemnity costs. The economic effects of product liability for medical products are a prominent issue in the policy debate concerning reform of the U.S. product liability system. Garber (1993, 1998) analyzed effects of medical products liability on various economic outcomes, Manning (1994, 1997) analyzed effects of product liability on drug prices, and Viscusi and Moore (1993) analyzed effects of product liability, not limited to medical products, on innovation. Whether the social benefits of such litigation (e.g., deterrence of inefficiently unsafe behavior) exceed the social costs (transaction costs of disputing, inducement of inefficient manufacturer decisions) for medical products or more broadly is unknown and controversial (e.g., Polinsky and Shavell, 2009).

Recently the Financial Accounting Standards Board (FASB) proposed, for the purposes of protecting investors, regulations that would require pharmaceutical companies to disclose estimated costs of on-going litigation. Industry leaders responded to this policy proposal negatively by asserting that subjective estimates would be unlikely to provide meaningful information given the volatile nature of product liability litigation (Favoli [is this spelling correct or the one in the reference list? please correct] and Mundy, 2008). An open question is the extent to which estimated effects of litigation events such as lawsuit filings, judicial rulings, trial outcomes and settlements on defendant firms’ stock prices and market values can be helpful in developing the information that the FASB proposed that manufacturers disclose to investors.

In this article, we examine effects of verdicts on product liability trials on the value of firms involved in medical product mass torts. We focus on trial verdicts because they are often very influential on the eventual defendant costs of mass torts in which thousands or tens of thousands of similar lawsuits involving a single drug or device are often resolved through settlements valued in large part on the basis of the outcomes of a handful of trials.
Trials, formally or informally used as “bellwether trials,” offer critical information about the realities of liability and damages for all pending and future claims to all parties involved in the mass tort (Barton, 1999; Rheingold 2008). For example, in the recent mass tort involving the prescription drug Vioxx, Merck reached a $4.5 billion settlement with tens of thousands of plaintiffs after sixteen trials in federal and state courts. This settlement cost, which was considerably less than many securities analysts’ initial estimates, is widely viewed as a result of Merck’s successful track record in Vioxx trials.9 Because a firm’s stock price reflects investors’ beliefs about the present value of the firm’s future profits—and litigation costs are part of those profit calculations—trial results in ongoing mass torts should, in principle, affect a firm’s stock price by changing investors’ beliefs about the firm’s future litigation costs.

This article is organized as follows. The next section reviews previous event studies of product liability litigation and argues that heterogeneity of events whose average effects are estimated obscures the meaning of reported results and greatly limits the applicability of these results to other sets of events. In section 3 we present a model for predicting stock-market reactions to outcomes of trial verdicts that emphasizes whether the defendant or the plaintiff prevailed at trial and, in the latter case, the size of the damage award. Section 4 uses the model to develop testable implications that are summarized by five hypotheses, and section 5 presents the regression equation we use to estimate the determinants of cross-verdict variation in (abnormal) stock-market reactions and test the hypotheses. Development of our data for 113 trials in nine medical product mass torts is discussed in section 6, and section 7 presents estimates of average percentage and dollar abnormal returns for our 48 and 65 sample verdicts for plaintiffs and defendants, respectively. We find large and statistically significant negative effects on stock prices and defendant firms’ values for plaintiff verdicts, but at best weak evidence of positive effects when defendants prevail at trial. Section 8 reports results of our regression analyses. Virtually all of the estimated regression coefficients are of the signs predicted by our model—most of the estimates pertaining to plaintiff verdicts are statistically significant, but most of the estimates pertaining to defendant verdicts are not. Concluding comments are offered in section 9.

9 Merck prevailed in twelve of the sixteen jury trials that reached a verdict. Three of the four plaintiff verdicts were overturned or the awards were subsequently reduced.
Section 2: Previous Event Studies of Product Liability Litigation

Several event studies—i.e., studies of stock-price reactions litigation events—have estimated wealth effects of product liability litigation. Only one of these studies focused entirely on trial verdicts. One possible reason is that this article (Garber and Adams, 1998) found no significant average market reactions for the automobile industry. Commentators have attributed the lack of effect to a variety of reasons. One explanation is that verdicts can be anticipated by investors and, thus, there is little, if any, new investor-relevant information when a verdict is announced (Peltzman 1998; Prince and Rubin 2002). This explanation, however, conflicts sharply with many anecdotal media reports about stock analysts waiting anxiously for outcomes of verdicts to update their litigation cost estimates for mass torts (e.g., in the context of Vioxx see Gold, 2006; Johnson, 2005a,b; Hays 2005).

Another potential explanation for the largely null findings of Garber and Adams (1998) about average wealth effects for plaintiff and defendant trial wins, however, is that their sample included two types of verdicts. The first type, which account for a majority of their sample, includes lawsuits that were not closely related to large numbers of other pending lawsuits against the defendant firms, and the second type involves lawsuits that were part of a larger set of similar pending claims (i.e., a “mass” tort). An empirical result supporting this interpretation is that while Garber and Adams did not find an overall average impact of plaintiff verdicts on firms’ value when pooling both types claims, they did find evidence that the second type of verdicts have a significant impact on defendant firms’ market value.10 Because we focus only on verdicts from medical product mass torts in this article, and numbers of claims in medical products mass torts are often orders of magnitude larger than those for motor vehicles, we believe the verdicts analyzed here are more likely to have a significant effects of firms’ value than those analyzed by Garber and Adams (1998).

---

10 In particular, in a regression analysis of cross-verdict abnormal returns associated with their sample of verdicts for plaintiffs, Garber and Adams (1998) include a variable indicating whether the existence of (presumably, fairly large numbers of) similar lawsuits were reported in the defendant firms’ SEC 10-K reports. This variable was found to be associated with larger (absolute) market responses to verdicts.
Other event studies of developments in product liability litigation focus on the automobile or pharmaceutical industry or both. These studies have produced mixed results. Table 2.1 summarizes major characteristics and results of these studies.

Table 2.1: Summary of Existing Product Liability Litigation Event Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Industry</th>
<th>Events</th>
<th>Sample</th>
<th>Event Windows</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscusi and Hersch (1990)</td>
<td>Auto and drug</td>
<td>Negative product safety news in Wall Street Journal - general</td>
<td>29 safety regulation violations or filings plus a series of filing or judge rulings in Agent Orange and DES mass toxic torts</td>
<td>day 0 (-4, +5)</td>
<td>Product liability lawsuits-related news had significant negative effects on firms sued</td>
</tr>
<tr>
<td>Garber and Adams (1998)</td>
<td>Auto</td>
<td>Trial verdicts</td>
<td>64 plaintiff verdicts, 116 defendant verdicts</td>
<td>(0,+1) (0,+2) (0,+3)</td>
<td>No significant market reaction</td>
</tr>
<tr>
<td>Prince and Rubin (2002)</td>
<td>Auto and drug</td>
<td>Initial filings Losing events Uphold events Pre-suit events</td>
<td>Auto: 15 initial filings, 25 other losing, 4 uphold Drug: 38 filings, 9 losing, 14 pre-suit</td>
<td>(-1,+1) (-5,-14)</td>
<td>Significant market reaction to filing events in auto industry and to pre-suit events in drug industry; no significant reaction to any other type of events</td>
</tr>
<tr>
<td>Govindaraj, Lee and Tinkelman (2008)</td>
<td>Auto</td>
<td>Initial filing Subsequent reports Resolution events</td>
<td>325 initial filings, 66 subsequent reports, 210 resolution events</td>
<td>(-1,+1)</td>
<td>No significant market reaction to any of the 8 types of events</td>
</tr>
</tbody>
</table>

* Day t=0 is the day when the event occurred, t < 0 indexes trading days before the event and t > 0 indexes trading days after the event.

The earliest study, Viscusi and Hersch (1990), examine the stock-market reactions to announcements in the *Wall Street Journal* of 29 events between 1970 and 1985 related to defective products. They also provide a brief examination of mass torts involving Agent Orange and the drug DES (diethylstilbestrol). They found significant negative impact of litigation events on the market values of firms involved. Prince and Rubin (2002) used samples of 44 auto-safety litigation events and 62 drug-safety litigation events. Overall they found significant negative market response associated with initial filing events but not with what they call “losing” events. Govindaraj et al. (2007) reexamine Prince and Rubin (2002)’s findings in the auto industry with an expanded sample of 609 litigation events. They found that after eliminating a single extraordinary litigation outcome involving Ford, stock market responses are no longer significant. They concluded that the market reacts only to the most extreme and infrequent litigation events.
A common feature of all of the studies discussed above is that, to varying degrees, analysts have treated sets of somewhat heterogeneous events as a single type and estimated average effects within such types. As just discussed, Garber and Adams (1998) combine verdicts in cases that are and are not members of larger sets of related cases. Moreover, the sample of Viscusi and Hersch (1990) includes safety regulation violations, lawsuit filings and judicial rulings. The “losing” events analyzed jointly by Prince and Rubin (2002) include both defendants’ losses at trials and adverse judicial rulings of various types. Finally, Govindaraj et al. (2008) include a category of “subsequent initial reports” which consist of reports of any product liability lawsuit claims, regardless of the context. Such aggregation over heterogeneous events fails to accommodate the possibility that different types of events within a somewhat heterogeneous set may affect investors’ beliefs about firms’ asset value through different channels and to substantially different degrees. Thus, the approaches in the existing literature fails both to offer meaningful estimates of average effects that would apply to other sets of events and to provide as much information as might be contained in the available data.

With the exception of Prince and Rubin (2002), the earlier studies use regression analysis to develop some insight concerning how event-specific characteristics affect the magnitude of stock market effect size (or lack of impact). For example, the estimates of Garber and Adams (1998) suggests that market responses to plaintiff verdicts are larger when damage awards are larger, when the Wall Street Journal reports the verdict, and (as discussed above) when investors have been informed similar pending cases through the firm’s SEC 10-K filings. Govindaraj et al. (2008) found that the market response appears to be larger when the estimated potential damage award associated with a lawsuit filing is larger. However, these econometric analyses are not based on any formal theoretical model of why and how a defendant firm’s value is affected by product liability litigation events. We address this gap in the current study.

Section 3: Litigation Costs, Trial Verdicts and Stock Prices: Theoretical Framework
A verdict in a trial that is part of a particular mass tort is expected to affect the stock price of the defendant firm to the extent that the verdict conveys new information to investors about the future costs of resolving claims in the same mass tort. When a defendant is found not liable at trial—an event that we refer to as a “defense win” or a “defense verdict”—the trial outcome is informative about the likelihood that unresolved claims within the mass tort will eventually be resolved by a compensation payment (either at trial or through settlement). Alternatively, when a defendant is found liable at trial—a situation we refer to as a “plaintiff win” or a “plaintiff verdict”—the trial outcome is informative about the likelihood of future compensation payments as well as the sizes of such future payments. More specifically, the size of the award announced by the fact finder (jury or judge) in the case of a plaintiff verdict also conveys to investors information about sizes of future compensation payments when such payments are made. We model investors’ beliefs in terms of subjective probabilities and use Bayes Rule to formalize how beliefs evolve or are updated as new information becomes available.

In medical product mass torts, the strategy of using verdict outcomes to estimate future litigation costs to the defendant—and the likelihood that such effects are large enough to be empirically discernible—is supported by the formal or informal practice of “bellwether” or “representative” trials. In particular, in a mass tort involving large numbers of similar claims, bellwether cases are usually selected by the Judge who oversees a consolidated federal or state mass tort. Although the specific methods used to select bellwether cases vary substantially from one mass tort to another, it usually involves some level of randomization and input from both the plaintiff and defendant steering committees, the groups of lawyers on each side who represent all of the lawyers on their side (Faulk et al. 1998; Sherman 2006; Fallon et al. 2008). The ultimate purpose of holding bellwether trials is often not to resolve thousands of related cases in “representative” proceeding, but instead to provide meaningful information and experience to inform lawyers on both sides of the strength or value of such claims, and this information is used to inform settlement negotiations (Fallon et al. 2008). In this section, we present a theoretical framework that characterizes the pathways through which a trial verdict in a mass tort would affect a defendant firm’s market value through stock-price reactions.
Consider a firm that is a defendant in mass tort $i$, and let the subscript $i$ denote the defendant firm as well as the mass tort.\textsuperscript{11} We start with a standard assumption that the value of a defendant firm $i$ at the close of trading day $t$—denoted by $V_{it}$—equals investors’ assessment of the present value of the firm’s expected future profits. We additively decompose this value into two parts, namely the present value of profits absent the mass tort (denoted by $\tilde{V}_{it}$) minus the present value of expected future costs of mass tort $i$ to the firm (denoted by $C_{it}$). Formally,

\begin{equation}
V_{it} = \tilde{V}_{it} - C_{it}.
\end{equation}

Let $\Delta_w$ be an operator denoting a change during an event window $w$, namely the change from shortly before to shortly after the announcement of a verdict.\textsuperscript{12} Then the change in the value of firm during an event window is the sum of two changes:

\begin{equation}
\Delta_w(V_{it}) = \Delta_w(\tilde{V}_{it}) - \Delta_w(C_{it})
\end{equation}

where $\Delta_w(\tilde{V}_{it})$ and $\Delta_w(C_{it})$ are, respectively, the changes during the event window in the value of the firm due to events that are not and are related to the eventual defendant costs of the mass tort. As is standard in event studies, we assume that—after netting out effects of general market movements during the event window\textsuperscript{13}— $E\Delta_w(\tilde{V}_{it}) = 0$. Thus

\begin{equation}
E\Delta_w(V_{it}) = -E\Delta_w(C_{it}).
\end{equation}

\textsuperscript{11} In our data, there are some firms that are defendants in more than one mass tort and a mass tort (silicon-gel breast implants) in which more than one firm was a defendant. Nonetheless, in the interest of notational economy, in this section, we use a single subscript to denote the firm and the mass tort.

\textsuperscript{12} For example, in our empirical work, we consider event windows of (i) one trading day before to one trading day after the day the verdict is announced (denoted by (-1,1)), and (ii) for sensitivity analysis purposes, also five trading days before to five trading days after the day the verdict is announced (denoted by (-5,5)). In the case of the (-1,1) window, the $\Delta_w$ operator is defined for any variable $X$ by $\Delta_w(X_{it}) = X_{it} - X_{it-1}$.

\textsuperscript{13} More specifically, and as detailed in section 6, we (following common practice in event studies) analyze empirically “abnormal” stock returns, which are deviations of actual (or observed) returns from the levels that would be predicted from general stock-market movements during the event windows.
or that the expected change in the value of a firm during an event window \( w \) (after accounting for general market movements during that time interval) is \textit{minus} the expected present value of the change during the event window of investors’ beliefs about the future costs to the defendant firm associated with the mass tort. Although the defendant’s litigation costs include both defense costs and indemnity (or compensation) payments, we focus on indemnity costs, assuming that investors’ forecasts of defense costs depends on factors that do not change during the event windows.

We model future indemnity costs as resulting from three factors that vary across time within a mass tort as well as varying across mass torts. These factors, whose product determines a defendant company’s future costs of a mass tort, are (i) the probability that a claim or lawsuit that has not yet been resolved will result in an indemnity payment, (ii) the size of an indemnity payment conditional on such a payment being made, and (iii) the number of claims that will be resolved in the future. We assume that—according to investors’ subjective beliefs—the probability of a payment being made (the first factor) is uncorrelated with the size of a payment when a payment is made (the second factor). We further assume, in this case for analytic convenience, that the eventual number of claims to be resolved is constant within an event window.

Invoking these assumptions allows us to write the investors’ expected present value of future indemnity payments as the product of three variables:14

\[
EC_{it} = \rho_{it} \times Y_{it} \times N_{it},
\]

where

\[
\rho_{it} = \text{the mean of investors’ subjective distribution as of day } t \text{ over the probability that a currently unresolved claim in mass tort } i \text{ will result in a payout},
\]

\[
Y_{it} = \text{the mean expected value of a payment given that a payment is made for a currently unresolved claim in mass tort } i,
\]

\[
N_{it} = \text{the mean expected number of claims to be resolved within the event window for mass tort } i.
\]

---

14 Writing the expected value of costs as a product of the expected values of the random variables \( \rho_{it} \) and \( Y_{it} \) (multiplied by the non-stochastic variable \( N_{it} \)) follows from the assumption that beliefs about the probability of future trial wins by plaintiffs are uncorrelated with beliefs about the size of the award given that there is an award. More specifically, when two random variables are uncorrelated, the expected value of their product is the product of their expected values.
\( Y_{it} \) = the mean of investors’ subjective distribution as of day \( t \) over the dollar size of the future indemnity payment per unresolved claim in mass tort \( i \) conditional on a payout, and

\( N_{it} \) = the eventual number of claims in mass tort \( i \), which we assume is fixed during an event window.\(^{15}\)

Regarding investors’ beliefs about the probability that a currently unresolved claim will eventually be resolved by a (compensation or indemnity) payment from the defendant to the plaintiff, we proceed as follows. We assume that the mean of investors’ subjective distribution over this probability, which we have denoted by \( \rho_{it} \), is determined by a function \( \rho_{it} = \rho(a_{it}, b_{it}) \), where \( a_{it} \) and \( b_{it} \) are the numbers of plaintiff and defendant trial verdicts, respectively, in mass tort \( i \) prior to the trial event under consideration. We assume \( \frac{\partial \rho_{it}}{\partial a_{it}} > 0 \) and \( \frac{\partial \rho_{it}}{\partial b_{it}} < 0 \), i.e., that a plaintiff verdict increases, and defendant verdict decreases, the mean of investors’ subjective distributions over the probability of payouts on claims that will be resolved in the future.

Regarding investors’ beliefs about the sizes of such future payments, we proceed as follows. First, we assume that \( Y_{it} \) is unaffected by information revealed by a defendant win at trial; this is because a defendant win at trial, which involves no award, reveals no new information about future payment sizes. In contrast, when the verdict under consideration is a plaintiff win, the size of the award does reveal new information about sizes of future payments. Accordingly, we assume that the mean of investors’ subjective distributions, which we have denoted by \( Y_{it} \), depends on the sizes of all past (non-zero) plaintiff awards in mass tort \( i \). Formally, \( Y_{it} = f(y_{it}) \), where \( y_{it} \) is a vector, with elements denoted by \( y_{it} \), containing the dollar values of all plaintiff awards in mass tort \( i \) observed through day \( t \). We assume that the function \( f \) is increasing in all of its arguments; i.e., the larger is any observed award, the

\(^{15}\) We impose this assumption because we have been unable to develop a satisfactory empirical method to account for changes in investors’ beliefs due to a verdict (equivalently, during the event window) about the number of claims to be resolved in the future (whether currently pending or yet to be filed).
larger is investors’ expected value of the size of a future payment (conditional on such a payment). Formally, the assumption is \( \frac{\partial Y_k}{\partial y_t} > 0 \).

With these additional assumptions, (4) can be rewritten as

\[
C_u = p(a_u, b_u) f(y_u) N_u. \tag{5}
\]

Our interest centers on how investors’ beliefs about the present value of expected future costs of mass tort change in response to two features of a new verdict, namely, (i) whether the trial resulted in a win for the defendant or a win for the plaintiff, and (ii) if the trial resulted in a plaintiff win, the size of the award. Suppressing the i and t subscripts (for notational simplicity) and differentiating (5) with respect to \( a \), \( b \), and \( Y \) yields,

\[
dC = \gamma N \frac{\partial P}{\partial y} \Delta_w(a) + \gamma N \frac{\partial P}{\partial b} \Delta_w(b) + LN Y \Delta_w(Y). \tag{6}
\]

Where \( dY = 0 \) when a trial results in a defendant win, and (generally) \( dY \neq 0 \) when the trial results in a plaintiff win.

Using (6) to approximate changes during event window w in the present value of expected future costs for discrete changes in \( a \), \( b \), and \( Y_w \), which we denote by \( \Delta_w(C) \), yields

\[
\Delta_w(C) = \gamma N \frac{\partial P}{\partial a} \Delta_w(a) + \gamma N \frac{\partial P}{\partial b} \Delta_w(b) + LN \Delta_w(Y). \tag{7}
\]

To interpret (7), consider the following.

**Verdicts for defendants.** When the event in window w is a defendant verdict, \( \Delta_w(a) = 0, \Delta_w(b) = 1 \) and \( \Delta_w(Y) = 0 \). Then, using (7), we have

\[
\Delta_w(C) = \gamma N \frac{\partial P}{\partial b}. \tag{8}
\]
Which is negative since \( Y > 0 \), \( N > 0 \), and \( \frac{\partial P}{\partial b} < 0 \). Thus, our model predicts that the defendant firm’s market value increases in response to the firm winning a trial since (see (3)), increases in expected future mass tort costs decrease firm value.

**Verdicts for plaintiffs.** When the event in window \( w \) is a plaintiff verdict, \( \Delta_w(a) = 1 \), \( \Delta_w(b) = 0 \) and \( \Delta_w(Y) \neq 0 \).\(^{16}\) Then, using (7), we have

\[
\Delta_w(C) = MN \frac{\partial P}{\partial a} + \rho N \Delta_w(Y),
\]

which is positive, (i) if (but not only if) \( \Delta_w(Y) > 0 \),\(^{17}\) or (ii) if \( \Delta_w(Y) < 0 \) and \( MN \frac{\partial P}{\partial a} > | \rho N \Delta_w(Y) | \). Thus, in principle, a defendant firm’s value could increase in response to losing at trial (i.e., \( \Delta_w(C) < 0 \) is possible even if the event is a plaintiff win) if the size of the verdict is small enough to reduce \( Y_t \) enough to overpower the tendency of firm value to decrease due to the increase in the expected probability of future plaintiff wins.\(^{18}\)

To summarize, our model assumes that trial verdicts in a mass tort affect a defendant firm’s market values through their effects on investors’ subjective beliefs about their effects on future litigation costs in the same mass tort. Whether the verdict is for or against the defendant firm—a dichotomous outcome—provides investors with additional information about the probability that any given claim against the defendant (that will be resolved in the future) will result in a payment. Moreover, the size of a trial award associated with a plaintiff verdict allows investors also to update their beliefs about the sizes of future payouts on claims that will be paid in the future. Because a plaintiff (defense) verdict generally increases (decreases) the mean of investors’ beliefs about the probability that any given claim will result in a payment, a plaintiff (defense) verdict is usually associated with a decrease (increase) in the firm’s market value. However, in principle, a plaintiff verdict could lead to an increase in firm’s value when the award size is sufficiently small.

\(^{16}\) Since verdicts for plaintiffs, unlike those for defendants, provide additional observations on award sizes that investors use to update their beliefs about \( Y \), in general \( \Delta_w(Y) \neq 0 \).

\(^{17}\) Since all of the other terms in (9) are positive.

\(^{18}\) For example, if \( Y_t = f(Y_{at}) \) were assumed to be the mean of past non-zero verdicts in mass tort \( i \), the size of the new verdict would have to be not only below the average award just prior to the latest verdict, but sufficiently below this average to reduce the average sufficiently.
Section 4: Testable Predictions about the Sizes of Market Reaction

Our model highlights major pathways through which a verdict affects a defendant firm’s stock price (market value). It also explains why, on average, we expect plaintiff verdicts to depress a defendant firm’s market value and defense verdicts to increase a defendant firm’s market value. A more intriguing question, however, is the circumstances under which we should expect a larger or smaller stock-market reaction when a new verdict occurs. We address that question in this section.

The sizes of the changes in the value of the firm in response to a new trial verdict are determined by the three exogenous variables, \(a\), \(b\), and (in the case of a plaintiff verdict) \(y_w\), which we use to denote the size of the trial verdict associated with event window \(w\).

To develop comparative static predictions for changes in \(a\), \(b\), and \(y_w\) consider defense and plaintiff verdicts in turn. For defense verdicts, differentiating (8) yields

\[
\frac{\partial \Delta_w(C)}{\partial b} = \gamma \mathcal{N}_w^2 p / \partial b^2 .
\]  
(10)

And for plaintiff verdicts differentiating (9) yields

\[
\frac{\partial \Delta_w(C)}{\partial a} = \gamma \mathcal{N}_w^2 p / \partial a^2 ,
\]  
(11)

and

\[
\frac{\partial \Delta_w(C)}{\partial y_w} = p \mathcal{N}_w(\gamma) / \partial y_w
\]  
(12)

Thus, the signs of the effects in (10) and (11) depend on the signs of second partial derivatives involving changes in means of investors’ posterior distributions for \(p\). And, according to (12), the sign of the effect of the size of a new award on future defendant costs of a particular mass tort depends on how the size of this award affects investors’ posterior
Effects of which party wins at trial. To determine the signs of the second derivatives in (10) and (11)—which we have not previously addressed\(^\text{19}\)—we specify and analyze Bayesian updating using an example of the function \(p_{lt} = \mathcal{P}(a_{lt}, b_{lt})\) that was introduced in the previous section. We adopt a commonly used specification to represent prior beliefs and sampling about a probability or proportion. Specifically, we assume that investors’ beliefs about \(p\) are given by a Beta distribution \(B(a, b)\), and that sample information about that probability (which are dichotomous) are governed by i.i.d. sampling from a binomial distribution. To specify beliefs about \(p\) before any verdicts (for a particular mass tort) are observed, we assume that that \(p\) is uniformly distributed on the \([0,1]\) interval,\(^\text{20}\) which corresponds to \(a = b = 1\). It follows that after observation of \(a + b\) trial verdicts (with \(a\) plaintiff wins and \(b\) defendant wins) the mean of investors’ posterior beliefs about \(p\) is

\[
p = p(a, b) = \frac{1+a}{2+a+b} \quad \text{\quad \text{(13)}}
\]

The result in (13) indicates that the posterior mean of \(p\) after \(a\) plaintiff verdicts and \(b\) defense verdicts is a nonlinear function of both \(a\) and \(b\). More specifically, (13) implies that while a plaintiff (defense) verdict generally increases (decreases) \(p\), it does so at a decreasing (increasing) rate. To establish these results, consider the following.

Differentiating (13) with respect to \(a\) and \(b\) yields

\[
\frac{\partial p}{\partial a} = \frac{1+b}{(2+a+b)^2} > 0 \quad \text{and} \quad \frac{\partial p}{\partial b} = \frac{-1-a}{(2+a+b)^2} < 0,
\]

\(^\text{19}\) The signs of the other terms in (10) and (11) have been addressed above.

\(^\text{20}\) We specify a uniform prior to represent a lack of prior information about \(p\) prior to observing any trial outcomes in the relevant mass tort.

\(^\text{21}\) See, for example, Hey (1983, pp. 110-120).
as assumed in the previous section. And, regarding second derivatives involved in (10) and (11), it follows that

\[
\frac{\partial^2 p}{\partial^2 a} = \frac{-2 - 2b}{(2 + a + b)^3} < 0, \tag{14}
\]

and

\[
\frac{\partial^2 p}{\partial^2 b} = \frac{2 + 2a}{(2 + a + b)^3} > 0. \tag{15}
\]

In sum, other things equal, we should expect (other things equal) a smaller absolute effect of a plaintiff (defendant) verdict on the stock market reaction as the number of previous plaintiff (defendant) verdicts increases in the same mass tort. Intuitively, as investors become more about more informed (from observing trial outcomes) about the probability that a claim will result in a payout, observations from additional trials will result in smaller and smaller updating of the mean for \( p \). We illustrate the relationships between \( a \) and \( p \) and \( b \) and \( p \) by a numerical simulation reported in Appendix A.

Combining results from the previous section and equations (10), (11), (14) and (15), we have the following testable hypotheses concerning which party wins at trial and the numbers of previous trial verdicts for plaintiffs and defendants.

**Hypotheses 1:** Holding constant the size of a trial award (if any), a plaintiff (defense) verdict will decrease (increase) the stock price of the defendant firm.

**Hypothesis 2:** The absolute size of the market reaction (in dollars) to a plaintiff verdict in a mass tort is smaller if more plaintiff verdicts have previously been announced in that mass tort.
Hypothesis 3: The size of the market reaction (in dollars) to a defense verdict in a mass tort is smaller if more defense verdicts have previously been announced in that mass tort.

Effects of award sizes. To consider effects of the size of the award when the plaintiff prevails, and generate testable predictions, we approximate investors’ prior beliefs about the size of the payout per claim (conditional on a positive payout), by a lognormal distribution; i.e., we assume that \( \ln Y \sim N(\mu, \sigma^2) \).\(^{22}\) It follows that after \( a \) i.i.d. observations on \( Y \), denoted by \( y_1, y_2, \ldots, y_a \), the posterior mean of investors’ subjective distribution over \( Y \) is

\[
Y = Y(\bar{z}) = e^{\bar{z}/(\sqrt{2}(\sigma + 1))} \sigma / (\sigma + 1),
\]

where, \( z_i = \ln y_i \), \( \bar{z} = \frac{1}{a} \sum z_i / a \), and \( \bar{z}^2 = \frac{1}{a} \sum (z_i - \bar{z})^2 / (\sigma + 1) \).\(^{23}\) i.e., that the posterior mean is a function of the mean of the logarithms of the observed award sizes.

The result in (16) reveals that, holding previous plaintiff award values constant, investors’ posterior belief about the size of \( Y \) is an increasing function of the natural logarithm of the new (or last) trial award \( z_a \). In addition, (16) implies that, holding constant the sizes of the previous awards, the larger is \( y_a \)—the size of the new award—the larger is \( z_a \) (since the logarithm is a monotonically increasing function) and the higher is the posterior mean of \( Y \).\(^{24}\) Thus, other things equal, the larger is a plaintiff award, the larger is the change in the mean of investors’ beliefs about the future indemnity payment per paid claim. In addition, as the size of the plaintiff award increases, investors’ beliefs about the mean indemnity payment per claim increases at a decreasing rate.\(^{25}\)

\(^{22}\) A lognormal distribution captures essential features (for our purposes) of the distribution of award sizes in civil trials, namely: (1) \( Y > 0 \) and (2) \( Y \) has a long tail on the right, i.e. some (fairly rare) verdicts have extremely large values. [can we find a study that documents a log-normal shape?]

\(^{23}\) See, for example, Hey (1983, pp. 160-175), and note that in our application it is \( \ln y_i \) that is normally distributed.

\(^{24}\) This follows from \( \frac{\partial Y}{\partial z_j} = \frac{1}{a} e^{\bar{z}/(\sqrt{2}(\sigma + 1))} \sigma / (\sigma + 1) > 0. \)

\(^{25}\) This follows from \( \frac{\partial^2 Y}{\partial z_j^2} = \frac{1}{a^2} e^{\bar{z}/(\sqrt{2}(\sigma + 1))} \sigma / (\sigma + 1) > 0. \)
Thus, we have the following empirical hypotheses concerning the effects of award sizes of defendant firms’ market values:

**Hypothesis 4:** The larger is the award, the larger is the absolute size of market reaction (in dollars) to a plaintiff verdict.

**Hypothesis 5:** The size of market reaction (in dollars) to an additional plaintiff verdict decreases in absolute value as the size of the plaintiff award increases.  

### Section 5: Empirical Model

Our basic model is a multiple regression with the dependent variables being $M_{ij}$, the change in firm i’s market value (in constant 2000 dollars) due to the jth verdict in mass tort i, from shortly before and to shortly after the jth verdict in that mass tort. Specifically, the regression equation we estimate is:

$$M_{ij} = \alpha_i V\text{P}_{ij} + \alpha_2 V\text{D}_{ij} + \alpha_4 A\text{WD}_{ij} + \alpha_5 V\text{P}_j \times P\text{L}_j + \alpha_3 V\text{D}_j \times D\text{F}_j + \alpha_6 A\text{WD}_j + \epsilon_{ij}$$

(17)

where,

- $V\text{P}_{ij} = 1$ if plaintiff wins in the jth verdict of mass tort i, 0 otherwise,
- $V\text{D}_{ij} = 1$ if defense wins in the jth verdict of mass tort i, 0 otherwise,\(^{27}\)
- $A\text{WD}_{ij} = $ dollar amount of plaintiff award in the jth verdict of mass tort i,
- $P\text{L}_{ij} = $ number of plaintiff verdicts in mass tort i prior to the jth verdict,
- $D\text{F}_{ij} = $ number of defendant verdicts in mass tort i prior to the jth verdict, and

\(^{26}\) Formally, the result is (from differentiating (12)),

$$\frac{\partial^2 Y}{\partial Z^2} = \frac{\partial^2 Y}{\partial Z^2} > 0,$$

which follows from

$$\frac{\partial^2 Y}{\partial Z^2} = \epsilon^{(1/2)(\alpha-1)} > 0.$$

\(^{27}\) Note that there is no intercept term in the regression; instead, we enter both VP and VD, which sum to one for each observation.
\[ e_{y} \] = the regression disturbance.

This regression equation is a translation of (7) where \( M \) corresponds to \(-\Delta w(c)\), \( VP \) corresponds to \( \Delta w(a) \), \( VD \) corresponds to \( \Delta w(b) \), and \( AWC \) corresponds to a monotonic positive function of \( \Delta w(Y) \). Moreover, the signs of the regression coefficients in (17) are predicted by the hypotheses developed above as follows:

1. \( \alpha_1 < 0 \) (Hypothesis 1),
2. \( \alpha_2 > 0 \) (Hypothesis 1),
3. \( \alpha_3 < 0 \) (Hypothesis 4),
4. \( \alpha_4 > 0 \) (Hypothesis 2),
5. \( \alpha_5 < 0 \) (Hypothesis 3), and
6. \( \alpha_6 > 0 \) (Hypothesis 5).

We report estimates of four versions of (17) in section 8.

Section 6: Data about Trials and Measures of Stock Market Responses

Using Lexis/Nexis and other sources,\(^{28}\) we collected information about trial verdicts and mass torts involving Bendectin, Fen-phen, Prempro, silicone-gel breast implants, Rezulin and Vioxx.\(^{29, 30}\) For each trial, we collected data such as whether the plaintiff or defense won at trial, damage awards, and cumulative number of plaintiff and defendant verdicts. The resulting sample includes 65 verdicts for which the defendant manufacturer was found not to be liable (“defense verdicts”) and 48 verdicts in which the manufacturer was held liable for money.

\(^{28}\) For example, web sites and SEC filings (10Ks, 10Qs) of defendant firms.
\(^{29}\) Four pharmaceutical companies were involved as defendants in the silicone-gel breast implants product liability litigation: Baxter International, 3M, Dow Corning and Bristol Myers Squibb. We consider such litigation against each of the four firms as a separate mass tort.
\(^{30}\) We limited our sample to mass torts with at least three trial verdicts and defendant companies whose stock is listed on the New York Stock Exchange. We excluded other medical product mass torts either because no trials occurred in that mass tort during our sample period—such as Zyprexa—or the defendant is a foreign company whose stock is not listed on the New York Stock Exchange—such as Accutane, Baycol and Sulzer hip and knee implants.
damages (“plaintiff verdicts”). Table 2.2 summarizes the basic statistics of these sample verdicts, all of which occurred between April 1981 and March 2008.

Table 2.2 Descriptive Verdict Statistics by Defendant Manufacturer

<table>
<thead>
<tr>
<th>Defendant</th>
<th>Product</th>
<th>Plaintiff Verdicts</th>
<th>Defendant Verdicts</th>
<th>Mean Damage Award*</th>
<th>Mean Damage Award**</th>
</tr>
</thead>
<tbody>
<tr>
<td>3M Co.</td>
<td>Silicone gel breast implants</td>
<td>3</td>
<td>4</td>
<td>1.68</td>
<td>3.69</td>
</tr>
<tr>
<td>Bax International</td>
<td>Silicone gel breast implants</td>
<td>2</td>
<td>14</td>
<td>2.50</td>
<td>4.25</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>Silicone gel breast implants</td>
<td>3</td>
<td>6</td>
<td>5.50</td>
<td>12.67</td>
</tr>
<tr>
<td>Merrell Dow Pharma***</td>
<td>Bendectin</td>
<td>7</td>
<td>10</td>
<td>4.45</td>
<td>21.74</td>
</tr>
<tr>
<td>Dow Corning***</td>
<td>Silicone gel breast implants</td>
<td>4</td>
<td>1</td>
<td>2.50</td>
<td>6.63</td>
</tr>
<tr>
<td>Merck</td>
<td>Vioxx</td>
<td>4</td>
<td>10</td>
<td>25.50</td>
<td>79.40</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Rezulin</td>
<td>4</td>
<td>4</td>
<td>17.49</td>
<td>20.00</td>
</tr>
<tr>
<td>Wyeth</td>
<td>Fen-phen</td>
<td>16</td>
<td>13</td>
<td>11.15</td>
<td>33.55</td>
</tr>
<tr>
<td>Wyeth</td>
<td>Prempro</td>
<td>5</td>
<td>3</td>
<td>8.75</td>
<td>28.55</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>48</td>
<td>65</td>
<td>9.80</td>
<td>27.36</td>
</tr>
</tbody>
</table>

* Compensatory damages only (in millions of 2000 dollars)
** Compensatory and punitive damages (in millions of 2000 dollars)
*** Merrell Dow Pharmaceutical was a subsidiary of Dow Chemical Co. Dow Corning is a joint venture between Dow Chemical and Corning Inc. We used Dow Chemical’s (NYSE: DOW) stock price to calculate abnormal returns for both mass torts.

We develop measures of abnormal changes in firms’ value using the standard event-study methods (MacKinlay 1997; McWilliams and Siegel 1997; Campbell 1998). Daily stock price data, adjusted for splits and dividends, were obtained from Yahoo Finance’s Historic Stock Price database. We estimated the normal (or expected) return on the defendant’s stock price using the “market model”:

\[ r_{it} = \gamma_i + \delta_i r_{mt} + \varepsilon_{it}, \]

where

\( r_{it} = \) percentage return on stock \( i \) from trading day \( t-1 \) to day \( t \), and

\( r_{mt} = \) percentage return on the Standard & Poor’s 500 Index from trading day \( t-1 \) to day \( t \) (our “market index”).

---

31 We excluded verdicts where there are multiple plaintiffs and the defendant was held liable for some but not all plaintiffs’ injuries (mixed verdicts). A total of 10 mixed verdicts were found in our original sample, primarily in the Fen-phen mass tort.
32 To convert all damage awards to constant 2000 dollars, we used quarterly GDP Price deflators available at http://research.stlouisfed.org/fred2/data/GDPDEF.txt.
The regression coefficients $\gamma_i$ and $\delta_i$ were estimated for each sample verdict using data from 200 trading days prior to the beginning of the verdict’s event window. We then constructed daily abnormal return, $AR_{it} = r_{it} - \hat{\gamma}_i - \hat{\delta}_i R_{mt}$ for days within two event windows of differing lengths defined as days (-1, +1) and days (-5, +5) respectively. We also construct CAR1 and CAR5, the cumulative abnormal return for the entire event window of (-1, +1) or (-5, +5) by summing $AR_{it}$ for days within the event window.

To construct CAVAL1 or CAVAL5, a measure of abnormal dollar returns expressed in millions of 2000 dollars, we multiple CAR1 and CAR5, respectively, by the average market capitalization of the company in the month before the relevant verdict.

Section 7: Average Wealth Effects of Verdicts

Table 2.3 reports summary statistics for four measures of stock market response separately for the 48 plaintiff verdicts and 65 defense verdicts. The standard errors used to assess the statistical significance of individual cumulative abnormal returns CAR1 and CAR5 were calculated according to a method summarized in Mikkelson and Partch (1988) and Salinger (1992). The significance of the average cumulative abnormal returns for all verdicts were

---

34 Thus the estimation window is from trading day -202 to trading day -2 for the first event window (-1, +1) and is from trading day -206 to trading day -6 for the second event window (-5, +5).
35 If the verdict was announced less than 200 trading days from previous verdicts, trading days within the event windows for previous verdicts were excluded from the estimation, and the estimation window was expanded backward to include a total of 200 trading days.
36 If the verdict was announced on a non-trading day (i.e., a Saturday, Sunday or holiday), the abnormal return variable incorporates the stock return over the following two trading days. If two verdicts for the same mass tort (and defendant in the case of breast implants) are announced within three days from each other, they are considered as one event and the event window comprises from one day before the first verdict to one day after the second verdict.
37 Market capitalization data were obtained from Standard & Poor’s Compustat North America database. The nominal values of market capitalization and other variables were adjusted using the quarterly GDP deflator.
38 The variance of CAR is calculated as $Var(CAR_{r}) = T \sigma^2 [1 + \frac{T}{U} + \frac{T}{U} \frac{r_{m0} - \bar{r}_m}{Var(r_m)}]$, where T is the length (in days) of the event window, $\sigma^2$ is the variance of $e_i$ in the market model, U is the lengths (in days) of the
tested by summing the t-statistics for individual CAR1 and CAR5 and dividing by the square root of the number of verdicts included. Because CAVAL1 (or CAVAL5) are simply products of CAR1 (or CAR5) and a firm’s market capitalization in the month before the verdict, we did not compute separate test statistics for CAVAL1 or CAVAL5.

Results in Table 2.3 provide evidence that plaintiff verdicts typically depress stock prices and defense verdicts typically increase them. The average abnormal return corresponding to plaintiff verdicts, as measured by percentage cumulative abnormal return CAR1 and CAR5, are both statistically significant. In our sample, a plaintiff verdict on average decreases the defendant firm’s stock price by 1.5 percent, which corresponds to an average loss in firm values of more than $908 million for 3-day event window (-1, +1). In contrast, the impact of defense verdicts on defendant firms’ values, as gauged by either CAR1 or CAR5, is not statistically significant. The sample means of cumulative abnormal returns by verdict type and by mass tort are reported in Appendix B.

Section 8: Regression Analysis of Cross-Verdict Variation in Abnormal Returns

The first column and second column of Table 2.4 report the results of estimating a restricted version the regression equation detailed in (17); in particular, these regressions include only the first three independent variables included in (17). The difference between the regressions corresponding to these two columns is that the variable AWD in first column includes only the compensatory damage award, but in the second column AWD includes the sum of the compensatory and punitive damage awards. Qualitatively, these results are consistent with the prediction from our model that plaintiff verdicts increase investors’ estimates about future litigation costs and thus depress the defendant firm’s market value. In addition, the estimates support the prediction that the larger a damage award, the larger is the market loss (because the estimated coefficients of AWD are negative and for column (1) statistically significant). Finally, defense verdicts appear to decrease investors’ estimates about future litigation costs

\[ estimation \text{ window, } \bar{r}_m \text{ and } Var(r_m) \] are the mean and variance of the market return over the estimation period of U.
Table 2.3: Summary Statistics for Cumulative Abnormal Returns

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaintiff verdicts (N=48)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR1</td>
<td>-0.015***</td>
<td>0.033</td>
<td>-0.123</td>
<td>0.054</td>
</tr>
<tr>
<td>CAR5</td>
<td>-0.0236**</td>
<td>0.065</td>
<td>-0.226</td>
<td>0.117</td>
</tr>
<tr>
<td>CAVAL1</td>
<td>-908.311</td>
<td>1698.270</td>
<td>-6080.587</td>
<td>2365.641</td>
</tr>
<tr>
<td>CAVAL5</td>
<td>-964.303</td>
<td>3257.869</td>
<td>-10884.560</td>
<td>6297.333</td>
</tr>
<tr>
<td>Defendant verdicts (N=65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR1</td>
<td>0.003</td>
<td>0.022</td>
<td>-0.045</td>
<td>0.062</td>
</tr>
<tr>
<td>CAR5</td>
<td>0.003</td>
<td>0.045</td>
<td>-0.091</td>
<td>0.179</td>
</tr>
<tr>
<td>CAVAL1</td>
<td>166.121</td>
<td>1200.230</td>
<td>-4613.383</td>
<td>5061.371</td>
</tr>
<tr>
<td>CAVAL5</td>
<td>217.998</td>
<td>1898.489</td>
<td>-7118.451</td>
<td>5969.930</td>
</tr>
</tbody>
</table>

*** t-statistic for CAR1 = -3.867, which is significant at 0.01 level.
** t-statistics for CAR5 = -2.523, which is significant at 0.05 level
Source: Author’s calculations. CAR and CAR5 are estimated cumulative abnormal returns during the (-1, +1) and (-5, +5) event windows, respectively. CAVAL and CAVAL5 are the cumulative dollar abnormal returns (in millions of 2000 dollars) during the same event windows, respectively.

and thus increase the defendant firm’s market value, although the estimated coefficients are not statistically significant.

Columns (3) and (4) report results from estimating all six regression coefficients in (17), adding to the regressors included in the equations whose results are reported in columns (1) and (2) the other three independent variables. The addition of these three independent variables improves the fit considerably; in particular, the $R^2$ values increase by 0.07 to .10, or roughly 50 percent relative the corresponding equations in columns (1) and (2). In the estimates reported in both columns (3) and (4), a plaintiff verdict is again associated with a significant decrease in the defendant firm’s market value and a defendant verdict is associated with an increase in the firm’s market value, although (as in columns (1) and (2)) in the latter case the estimated regression coefficients are not statistically significant at the 0.05 level. In both cases, AWD has a significant negative effect on the firm’s market value, as hypothesized.
Table 2.4: CAVAL\_1 Regressed on Independent Variables

<table>
<thead>
<tr>
<th>Explanatory Variables</th>
<th>Predicted sign</th>
<th>Coefficients (t-ratios)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1)(^a)</td>
<td>(2)(^b)</td>
<td>(3)(^a)</td>
<td>(4)(^b)</td>
</tr>
<tr>
<td>VP</td>
<td>-</td>
<td>-708***</td>
<td>-807***</td>
<td>-695**</td>
<td>-795***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-3.14)</td>
<td>(-3.66)</td>
<td>(-2.13)</td>
<td>(-2.78)</td>
<td></td>
</tr>
<tr>
<td>DP</td>
<td>+</td>
<td>166</td>
<td>166</td>
<td>397</td>
<td>397*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.96)</td>
<td>(0.94)</td>
<td>(1.67)</td>
<td>(-1.68)</td>
<td></td>
</tr>
<tr>
<td>AWD</td>
<td>-</td>
<td>-11.8**</td>
<td>-1.98</td>
<td>-47.9**</td>
<td>-16.1***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-2.22)</td>
<td>(-1.44)</td>
<td>(-2.53)</td>
<td>(-3.48)</td>
<td></td>
</tr>
<tr>
<td>VP×PL</td>
<td>+</td>
<td>28.6</td>
<td>40.2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.17)</td>
<td>(1.85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VD×DF</td>
<td>-</td>
<td>-21.6</td>
<td>-21.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-1.37)</td>
<td>(-1.38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWD(^2)</td>
<td>+</td>
<td>-0.211*</td>
<td>0.0153***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td></td>
<td>0.19</td>
<td>0.17</td>
<td>0.26</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>113</td>
<td>113</td>
<td>113</td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\): AWD includes only compensatory damage award (in millions of 2000 U.S. dollars).
\(^b\): AWD includes both compensatory and punitive damage awards (in millions of 2000 U.S. dollars).

*: significant at 0.10 level

**: significant at 0.05 level

**: significant at 0.01 level

The coefficient of the interaction term VP×PL indicates how the effect of a plaintiff verdict depends on the number of previous plaintiff verdicts in the same mass tort. Results in column (3) indicate that other things being equal, the stock market loss associated with a plaintiff verdict is $28.6 million smaller for each previous plaintiff verdict, although this estimate is not statistically significant. The corresponding estimate in column (4) — i.e., when AWD, the measure of the award size includes both compensatory and punitive damages—is to $40.18 million and is statistically significant at the 0.1 level. These results are consistent our prediction in Hypothesis 2 that the impact of a plaintiff verdict on firm’s value decreases (absolutely) as the number of earlier plaintiff verdicts in the same mass tort increases.
Similarly, the coefficients of the interaction term $VD \times DF$ indicate how the impact of a defense verdict varies with the number of previous defense verdicts in the same mass tort. Results in both column (3) and (4) indicate that, other things being equal, the gain in defendant firm’s market value is lower by $21.6$ million for each previous defense verdict. Although this coefficient is statistically significant in neither column, its negative sign is consistent with our prediction in Hypothesis 3.

Finally, a negative coefficient of the variable $AWD^2$ (the square of the award sizes) would indicate—as predicted by Hypothesis 5—that the rate of decrease in firm’s market value when $AWD$ increases declines as the award size increases. This prediction is supported by a significantly negative coefficient of $AWD^2$ in column (3). However, in column (4) the estimated coefficient of $AWD^2$ is positive.

**Section 9: Conclusion**

Stock-price reactions to litigation events may be a promising way to help in forecasting future costs of litigation to defendant companies. Lessons available from previous studies of events in product liability litigation are limited by the averaging of stock-price reactions over disparate types of events, casting doubt on the applicability of previous findings to other litigation events of the same broad type. In this article, we propose and apply a more rigorous approach to analyzing abnormal returns associated with litigation events, focusing on a special, but especially important, type of product-liability litigation event—trial verdicts in cases that are part of mass torts.

In particular, we propose a simple, formal model of the determinants of the sizes of stock-market reactions to verdicts in medical products mass torts. In many such mass torts, trials are used to develop a better sense of how juries react to evidence of negligence on the part of the defendant company and how they view appropriate levels of damages. And in many medical product mass torts, settlement negotiations involving thousands or tens of thousands or even hundreds of thousands of pending claims are substantially informed by the outcomes of a handful of trials. Thus, outcomes of individual trials can have very substantial implications.
for settlement values and the eventual costs to defendants of resolving pending and future claims.

According to our model, investors focus on the future costs of paying claims and update their beliefs (using Bayes Rule) in response to trial outcomes in each mass tort. The model emphasizes, and leads to refutable predictions about, effects of (i) whether the plaintiff or defendant prevailed at trial, (ii) the size of the award associated with a plaintiff verdict, and (iii) the numbers of previous plaintiff and defendant wins at trial in the same mass tort.

Our data pertain to 113 trial verdicts in nine mass torts during the period April 1981 to March 2008, with defendants and plaintiffs prevailing in 65 and 48 trials, respectively. We find that on average, plaintiff wins depress defendants’ stock prices by about 1.5 percent, or roughly $900 million (2000) dollars, a result that is highly statistically significant. Our point estimates of the average effect of defendant wins at trial suggest that stock prices increase, but only by 0.3 percent (or roughly $200 million), and these estimates are not statistically significant. One potential explanation for our finding larger (and less equivocal) impacts of plaintiff verdicts is that (more often than not) shortly before a trial ends in a verdict, investors assign a probability substantial greater than one-half to defendant (i.e., plaintiff wins are typically more surprising to investors than are defendant wins).

Multiple regression analyses of cross-verdict variation in abnormal dollar returns to our sample verdicts provides considerable support for five testable hypotheses derived from our theoretical model. Not surprisingly given our results on average market responses to verdicts for defendants and plaintiffs, our regression results are considerably stronger with regard to theoretical predictions for plaintiff verdicts. These include economically substantial and statistically significant estimates (of the signs predicted by the model) of the effects of plaintiff verdicts and the sizes of the associated damages awards, but mixed evidence concerning whether the marginal effect of award size decreases as the award size increases. None of our estimates pertaining to effects of defendant verdicts is statistically significant at the 0.05 level, but all of the associated point estimates are of the signs predicted by our model. More specifically, the estimates pertaining to effects of defendants win at trial are
positive—suggesting an average investor loss of almost $400 million 2000 dollars—with p-values of about 0.1, and a smaller impact of a defendant verdict the larger is the number of previous defendant verdicts in the same mass tort.

Our basic approach and methods have several limitations, both in our empirical application and for extension to other types of litigation events. Our approach involves focusing on homogenous types of litigation events that would plausibly affect stock prices by econometrically discernible amounts. We chose to focus on trial verdicts in medical products mass torts, largely because the stakes in individual trials can be exceptionally high. Our set of sample events, however, is not entirely homogenous, and we have been able to control for only some important sources of heterogeneity with variables that could be accurately measured and incorporated in a regression analysis (i.e., the winning party, the size of the award, and numbers of previous trial victories for each side). Most troubling in this regard, it seems, are (i) that we do not control for differences across our sample mass torts in the numbers of claims that have yet to be resolved, which includes both currently pending claims and future claims that have yet to be filed; and (ii) we do account for potential effects of trial outcomes on numbers of future filings.

Extending our general approach to studying stock-market reactions to other events in product-liability litigation confronts several challenges. Most challenging, it seems, are identifying other types of litigation events that are sufficiently (i) homogenous or whose heterogeneity can be adequately controlled with observable variables, and (ii) numerous to permit econometric analysis—over almost three decades, our sample includes only a modest number of trial verdicts. Thus, it is an open question whether the kind of analyses we have conducted can be fruitfully adapted and applied to the study of other types of litigation events.

References


Appendix A: Comparative Statics of Bayesian updating result for

Figure 2.1: Predicted Change in $p$ as Number of Verdicts Increases

In Figure 2.1, the Y axis is the projected size of $\frac{\partial p}{\partial a}$ (triangles) or $\frac{\partial p}{\partial b}$ (diamonds) and the X axis is the number of cumulative plaintiff verdicts or defense verdicts. When calculating $\frac{\partial p}{\partial a}$, we assume $b=1$ for all values of $a$. Similarly, when calculating $\frac{\partial p}{\partial b}$, we assume that $a=1$ for all values of $b$. 
# Appendix B

Table 2.5: Sample Means and Standard Deviations for Cumulative Abnormal Returns by Verdict Type and by Mass Tort

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAR1</th>
<th>CAVAL1</th>
<th>CAR5</th>
<th>CAVAL5</th>
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<td><strong>Plaintiff verdicts</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3M. Co.</td>
<td>-0.016</td>
<td>-172.080</td>
<td>-0.056</td>
<td>-763.089</td>
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<td></td>
<td>(-1.22)</td>
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<td>0.000</td>
<td>1.645</td>
<td>-0.037</td>
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<tr>
<td></td>
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<tr>
<td>Bristol-Myers Squibb</td>
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<td>-0.007</td>
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<td>-0.020</td>
<td>-200.029</td>
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<td>0.009</td>
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<td></td>
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<td>(0.20)</td>
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<tr>
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<td><strong>Defendant verdicts</strong></td>
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<td>-81.674</td>
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<td></td>
<td>(0.18)</td>
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<td>Wyeth (prempro)</td>
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Essay 3

Combating Unsafe Drugs: China’s Progress and Problems$^{39}$

$^{39}$To be submitted to an academic journal with Wei Wilson Zhang as a co-author.
Section 1: Introduction

The Chinese pharmaceutical industry has experienced tremendous growth in recent years, fueled by rapidly growing domestic consumption and accelerating global demand for inexpensive pharmaceutical ingredients. Between 1998 and 2007, the total output of Chinese pharmaceutical production increased from $16.5 billion to $86.7 billion. During the same period, the total value of Chinese pharmaceutical exports increased from $3.4 billion to $14 billion [1] (Figure 3.1). At present, China is one of the world’s largest pharmaceutical ingredient suppliers. Together with India, it supplies 40% of active pharmaceutical ingredients (APIs) consumed in the U.S. and 80% in Europe [2, 3].

China’s fast growing pharmaceutical sector could potentially help to lower global drug prices and improve consumer welfare. However, it also generates significant challenges to drug safety regulators at home and abroad. China-originated counterfeit and substandard drugs have flourished thanks to insufficient regulatory oversight, weak legal institutions and a domestic market that does not incentivize strict compliance with safety standards. The resulting episodes of high profile drug safety problems, which occurred during 2006-2008 both within and outside China, have brought Chinese drug safety under intense public scrutiny. Under pressure from both the domestic population and foreign trading partners, China has since taken promising steps to overhaul its regulatory framework. This rapidly evolving regulatory environment has inevitably led to uncertainty as regulators and businesses alike struggle to understand the impacts and deficiencies of policy interventions.

Drawing evidence from an extensive review of the literature and interviews with high-level Chinese regulatory officials (see Appendix A), we review key policy changes and seek to identify remaining issues as well as areas of future promise within China’s drug safety regulatory system. It should be noted that drug-related injuries can result from different types of safety problems.40 This paper focuses on safety problems inherent in the drug itself (such

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40 First, drug safety problem might be caused by manufacturing defects, such as substandard ingredients, improper sterilization or package contamination, which are dangerous to the drug’s users. Second, the safety problem can be inherent in the chemical properties of the drug even when properly manufactured. For example, various drugs are believed to cause injuries (e.g. heart attack, stroke, breast cancer etc.) in a proportion of its
as the chemical properties of the drug or manufacture defects) rather than those resulting from user problems (including not being used as directed or being used among unacceptably risky populations). In so doing so, we hope to concentrate our discussion on the regulation of the pharmaceutical industry, since it is the most critical player in China’s recent drug safety crisis.

Figure 3.1: Chinese pharmaceutical output and exports 1998-2007

Sources: China Pharmaceutical Year Books 2002-2008

Section 2: A Brief History of Pharmaceutical Regulation in China

The enactment of the Pharmaceutical Administrative Law (PAL) in 1984 marked the beginning of China’s modern-day drug safety regulation [1]. While previously drug makers could easily receive drug manufacturing licenses from provincial health departments, the new law required companies to conduct systematic pre-marketing testing to prove the safety and efficacy of their drugs. During 1984-1998, drug safety oversight duties were shared by three national regulatory agencies, namely, the Ministry of Health's (MOH) Drug Administration Bureau, the State Pharmaceutical Administration Bureau, the State Administration of Traditional Chinese Medicine.

users even though the drug appears to be safe in clinical trials that involve a limited number of users. Finally, injuries can be caused by drugs because they are prescribed to people for whom the drug is unacceptable risky (e.g. pregnant women, people with abnormal liver function, people who are taking drugs that interact badly with the drug in question.) or because the drug is not used as directed (e.g. above or below recommended dosage).
In 1998, an independent regulatory authority, the State Drug Administration (which later became the State Food and Drug Administration, or SFDA), was established to provide a unified authority for drug safety regulation. Using the U.S. Food and Drug Administration (FDA) as a model, the SFDA oversees the development, manufacture, distribution and marketing of all pharmaceutical products, biomedical products, Chinese traditional medicine and medical devices [4]. It also provides regulatory leadership to thousands of provincial and municipal drug departments who are responsible for carrying out routine market and manufacture inspections and assisting the SFDA to collect and screen new drug applications. Provincial and municipal drug departments, however, maintain a substantial level of independence from the SFDA, partly because they also receive oversight from the provincial government within whose jurisdiction they are located.

During its first ten years, the SFDA embraced a host of reforms that replaced various provincial regulations with uniform national standards. It also expanded its regulations from covering only drug registration and inspection to governing the entire supply chain of pharmaceutical production, including both pre-marketing drug evaluation (preclinical, clinical and new drug approval) and post-marketing safety surveillance (production quality control, distribution and adverse drug reactions or ADRs monitoring). Table 3.1 presents an overview of the current SFDA regulatory framework [1, 5, 6]. SFDA requires preclinical laboratory and animal studies and clinical trials (phase I, II and III studies) to be conducted based on national Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) guidelines starting in 2007 and 2004, respectively [5, 6]. Once a new drug goes through these trials, the SFDA evaluates the results submitted by the manufacturer/developer and decides whether the drug should be approved for marketing according to safety and efficacy standards set forth by the Provisions on Drug Registration (PDR). Since 2004, SFDA mandates manufacturers to comply with the national Good Manufacture Practice (GMP) which specifies how drugs should be manufactured to ensure safety, efficacy and quality. The SFDA also enacted quality control standards for distributors, i.e. the Good Supply Practice (GSP) in 2002. For drugs that are already in the market, the SFDA and its provincial counterparts conduct routine quality inspections at manufacturing sites as well as retail outlets. Starting in 2004, SFDA adopted a national Adverse Drug Reactions (ADRs) monitoring system that requires manufacturers,
distributors and health care providers to monitor and report adverse drug reactions (ADRs) to provincial or national ADRs monitoring centers.

The true impact of the SFDA’s efforts to build a comprehensive drug safety framework is difficult to measure, particular since China has not collected data on drug safety in any systematic way. Indirect evidence shows that progress has been made in several areas. For example, about 4,000 drug manufacturers who failed to pass the national mandatory GMP certification were forced to close down by June 2004 [1]. Unofficial reports circulated by Chinese media indicate that the share of counterfeit and substandard drugs sold in the market decreased from about 18% in 1997 to less than 2% in recent years [7]. Meanwhile the number of ADRs reports received by the SFDA increased from less than 5,000 in 2001 to more than 360,000 in 2006 [8, 9].

Table 3.1: Overview of SFDA’s Regulatory Framework

<table>
<thead>
<tr>
<th>Stage</th>
<th>Preclinical</th>
<th>Clinical</th>
<th>Approval</th>
<th>Production</th>
<th>Distribution</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities</td>
<td>Toxicology study</td>
<td>Safety, dosage, efficacy, side effects</td>
<td>Clinical results, manufacture license</td>
<td>Process control, validation, documents</td>
<td>Warehouse &amp; transportation quality control</td>
<td>Post-marketing surveillance</td>
</tr>
<tr>
<td>Standards</td>
<td>Good Laboratory Practice (GLP)</td>
<td>Good Clinical Practice (GCP)</td>
<td>Provisions for drug registration (PDR)</td>
<td>Good Manufacture Practice (GMP)</td>
<td>Good Supply Practice (GSP)</td>
<td>The Rule on ADRs Reporting (ADRs Rule)</td>
</tr>
</tbody>
</table>

In addition to the SFDA, China’s National Development and Reform Commission (NDRC) also plays an important role in shaping China’s pharmaceutical policy. NDRC and its provincial counterparts set maximum domestic retail prices for prescription drugs in the Essential Medicine list and various national and provincial health insurance drug lists [10]. New drugs are generally exempted from price regulation to encourage innovation [11]. However, because the SFDA had defined “new drug” broadly as drugs that have not been marketed or sold in China, rather than for example new chemical entities (NCEs) that have not previously been approved for human use in the U.S. or other countries, manufacturers were able to obtain the so-called new drug status for existing generic drugs simply by
Section 3: Drug Safety Crisis in 2006-2008

Despite China’s progress in modernizing its drug safety regulation, a series of high profile drug safety incidents broke out beginning in 2006 and quickly evolved into an international crisis. The first domestic incident occurred in April 2006 when 11 people died and more were injured from an injection of Armillarisin A that was produced with substandard propylene glycolin by the Qiqihar No.2 Pharmaceutical Co. Ltd [14]. Four months later, at least 11 more people died in China from an antibiotic injection called clindamycin phosphate glucose due to its not having been properly sterilized by its producer Anhui Huayuan Worldbest Biology Pharmacy Co. [15]. In July 2007, nearly 200 Chinese leukemia patients were sickened by Methotrexate & Cytarabine injection contaminated with Vincristine Sulfate that was manufactured by Shanghai Hualian Pharmaceutical Co. [16]. A year later, an herbal injection called Wu Jia Ci that was contaminated during distribution claimed at least three lives and injured dozens in Yunnan province [17]. Outside of China, more than 100 people reportedly died in early 2007 in Panama after consuming cough medicine contaminated by diethylene glycol that was produced in China [18]. Also in the same year, 95 Americans died from anticoagulant Heparin believed to have been contaminated by raw materials produced in China [19]. Although the exact cause of the Heparin deaths was disputed by Chinese authorities, this case received great attention from both the U.S. government and the mass media, and brought substantial negative publicity about Chinese pharmaceutical products in general.

Section 4: Responding to the Crisis - China’s Regulatory and Legal Changes

In the wake of the high profile drug safety failure, the Chinese government has moved quickly to introduce an overhaul of its regulatory and legal institutions to rebuild public confidence in China’s pharmaceutical products. Major policy interventions include tightening market entry control by raising standards for new drug approval, enhancing the production...
quality control through rewriting the GMP guidelines, expanding post-market ADRs surveillance, introducing a national drug recall system and increasing the criminal penalties for producing and selling counterfeit and substandard drugs. Each of these regulatory developments is discussed in turn in this section.

4.1. Raising the Bar for New Drug Approval

New drug approval was the first focus of post-crisis reform, thanks to extensive media reports about the abuse of approval authority by the former SFDA Head Zheng Xiaoyu. According to a widespread news report, the SFDA approved 19,000 new drug applications in 2004. In the same news article, this figure was compared to 148 that were approved by the U.S. FDA in the same year to highlight the lack of rigor in SFDA’s new drug evaluation [20].41 After the two deadly drug incidents that happened in April and August 2006, the SFDA drastically tightened the technical standards for new drug applications. As a result, the annual number of applications filed with the SFDA dropped by nearly two thirds (Figure 3.2). In October 2007, SFDA officially raised the bar for new drug approval through a revised version of PDR. Among other things, the new PDR requires SFDA to take steps to confirm the clinical information filed in support of a new drug application, to inspect the manufacturer’s production site, and to improve collection of samples by taking samples at the site of manufacturing instead of relying on samples sent by the applicant, as was the case in the past [21-23]. The new PDR also prevents manufacturers from obtaining the “new drug” status by changing dosage, route of administration or inactive ingredients of existing products.42 Such practice had been common in the past to avoid NDRC’s retail price caps. With these new measures, approval rate for new drug applications has reportedly fallen from 80% to 37% [21].

41 The large difference between the number of news drugs approved in China and the U.S. is obviously also due to SFDA’s broad definition of new drug.
42 NCEs and generics that have been marketed abroad but not in China are still both considered new drugs.
4.2. Re-Examining Existing Drugs, Manufactures and Distributors

In addition to strengthening the standards for new drug approval, SFDA launched a six-month national “clearing house” campaign [24]. By July 2007, the government announced that it had re-examined more than 28,204 drugs and revoked 578 drug licenses [25]. The SFDA also withdrew from 128 manufacturers of their GMP certifications and ordered another 2,025 manufactures – nearly one third of all manufacturers – to correct violations of the GMP code within specified time periods [25]. In addition, the SFDA inspected 89.6% of drug distributors and retailers nationwide, which resulted in the loss of GSP certifications by 481 distributors and the discovery of 3,325 illegal distributors and retailers [25]. As an extension of this campaign, the new PDR adds a provision that requires all previously approved drugs to re-register every five years [26]. The application package for re-registration must include information about phase IV clinical trial results and evaluation of ADRs. Nationwide re-registration officially began in July 2009 and is expected to be completed for all drugs...
approved prior to 2006 by September 30, 2010 [26]. Drugs approved after 2006 will be expected to comply with the new regulations once their five-year marketing periods end.

4.3. Tightening Production Quality Control

China introduced Good Manufacture Practice (GMP) for manufacturing and quality control of pharmaceutical products in the early 1990s. In 2004, about 6,000 pharmaceutical companies passed the nationwide mandatory GMP certification [1]. However, unlike the U.S. FDA’s current GMP (cGMP) standards and the European Medicines Agency’s (EMEA) GMP standards, the Chinese GMP guideline primarily focused on production facilities and equipment while overlooking critical issues such as quality control, risk analysis, personal hygiene, ongoing stability checking and process validation [2]. To better align the Chinese GMP Guideline with international standards, SFDA issued a new GMP guideline in September 2007 [27]. The new guideline greatly expands technical requirements for personnel qualifications, production processes, quality control and validation documentation. Another highly publicized new addition is the requirement for each manufacturer to have a designated Quality Authorizer to ensure quality standards are met throughout the production process [28]. Besides tightening GMP standards, SFDA hired more GMP inspectors to carry out scheduled as well as unannounced GMP inspections. Specifically, the number of GMP inspectors grew by more than 50% from 1,715 in 2006 to 2,629 in 2008 [29, 30].

4.4. Expanding Post-Marketing Surveillance

Adverse drug reaction (ADR) usually refers to “harm associated with the use of a drug at normal dosage for intended purposes” [31]. Although it is often difficult to determine the exact cause of such reactions, systematic monitoring of ADRs may provide essential information about a new drug’s safety and effectiveness under real-life conditions that was not detected during clinical trials [31]. Policymakers worldwide therefore rely heavily on analysis of ADRs to make evidence-based decisions about labeling change, package modification or recalling of a drug. China did not have a national ADRs monitoring system until 2004, when the first national Rule on ADRs Reporting and Monitoring (the “ADRs
Rule”) was established [1]. Since then, China has made great strides in increasing the number of ADR events reported, although it still lags significantly behind the U.S. in terms of numbers of ADR reports per million people [32-34]. (Figure 3.3) One particular issue is that despite China’s ADRs Rule requiring all drug manufacturers, distributors and health care providers to report ADRs within specified time frames, Chinese drug manufacturers have historically lacked incentives to fulfill their obligations to report ADRs. For example, Chinese drug makers contributed less than 10% of all ADRs reported during 2004-2007, far less than 90% in the U.S. and other countries despite having largely the same set of reporting protocol [32]. In June 2009, SFDA issued a new draft revision of the Rule on ADRs Reporting and Monitoring (the New “Rule”) [35]. The proposed new Rule expands the scope of events that are required be reported to include not only ADRs, but also all Adverse Drug Events (ADEs), as is the case in the U.S. [34].43 The new Rule shortens the timeline within which an event must be reported and places an increased reporting burden on manufacturers. If a drug is confirmed to have caused severe ADRs by the national ADR Monitoring Center, the drug manufacturer is now required to take timely actions to communicate with physicians, patients and the public, revise drug packaging, labels and product inserts, or recall the drug if necessary.

4.5. Launching a National Drug Recall System

Progress in building a national ADRs reporting network from 2004 to 2007 provided an opportunity for the SFDA to launch China’s drug recall system based on post-marketing surveillance. In December 2007, SFDA officially introduced the first national drug recall system [36]. Following international practice, drug recalls are classified into three levels with varying severity: Category 1 Recalls involve drugs that can potentially cause severe injuries or even death and should be issued within 24 hours of the announcement; Category 2 Recalls involve drugs that may cause temporary or reversible health problems and should be issued within two days; Category 3 Recalls involve drugs that must be recalled within three days for

43 Adverse Drug Event (ADE), is defined broadly as “all medical events occurred during a pharmaceutical treatment that are harmful and suspected to be related to the use of a drug”. The difference between ADR and ADE lies in that the latter does not assume that the adverse outcome to have occurred at normal doses for intended uses.
reasons other than safety, such as improper packaging. Manufacturers are given incentives to withdraw problematic drugs voluntarily, namely lower fines and administrative punishment or even avoid paying any fines or punishment. Those who are aware of problems with their drugs but fail to issue voluntary recalls will face fines of up to three times the value of the recalled drugs or even be deprived of drug-manufacturing licenses.

Figure 3.3: Number of ADRs/ADEs Reported per Million People by Year

![Bar chart showing the number of ADRs/ADEs reported per million people by year, with data points for China and U.S.]  
Sources: SFDA Annual ADRs reports and FDA Adverse Event Reporting Systems (AERS) statistics

4.6. Expanding Criminal Prosecution for Producing or Selling Counterfeit and Substandard Drugs

The majority of China’s drug safety incidents, including high profile scandals that occurred between 2006-2008, involve counterfeit and substandard drugs, i.e. drugs whose composition and ingredients do not meet the correct technical specifications and which are consequently ineffective and often dangerous to patients [37].  

44 This is significantly different from the U.S. and other developed countries where counterfeit and substandard drugs are rare and drug safety injuries occur primarily because of ADRs/ADEs associated with NCEs that are recently sold in the market

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44 This is significantly different from the U.S. and other developed countries where counterfeit and substandard drugs are rare and drug safety injuries occur primarily because of ADRs/ADEs associated with NCEs that are recently sold in the market
when the products cause serious injuries [38]. In May 2009, China’s Supreme People’s Court and Supreme People’s Procuratorate jointly released a new Special Judicial Interpretation of the 141st and 142nd Clauses of the Chinese Criminal Law [39]. Under the new interpretation, physicians who knowingly prescribe and sell counterfeit or substandard drugs will be prosecuted as accomplices as will individuals or companies who supply capital, raw ingredients, shipping services, storage, packaging, advertisement or other services for the production or sales of counterfeit or substandard drugs despite knowing the drugs are counterfeit or substandard. This Interpretation provides a detailed list of criteria to define prosecution thresholds based on the severity of “injuries and health problems”.

Section 5: How Well Will the New Policies Work?

Pharmaceutical safety control is a complex process within which governmental regulations interact with market incentives to determine the level of safety investment private companies should choose to make. In regulatory economics, corporate compliance behavior is considered to be influenced by the strengths of regulation as well as by the market reward for good compliance [40]. SFDA’s post-crisis regulation overhaul, from this broader perspective, should be viewed as an important step forward towards raising the minimum safety standards deemed necessary by the government. The success of these governmental interventions in improving China’s drug safety will rely on at least two key conditions: first, rigorous enforcement of existing and new government regulations; and second, a market that rewards safe drugs and punishes unsafe drugs. In this section, we identify key barriers and areas of promise for each of these two conditions.

5.1. Barriers and Promise for Effective Regulation Enforcement

Governmental Enforcement Capacity

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45 The Supreme People’s Procuratorate is China’s highest law enforcement agency, analogous to the U.S. Department of Justice.
Insufficient resources have historically been a major contributing factor to China’s weak drug safety regulatory enforcement. According to a speech by China’s Vice Premier Wu Yi in 2005, “80% of municipal and local drug departments did not have fixed office space and the majority of them lacked adequate testing, inspection and transportation equipment to carry out routine quality and safety control activities they were required to conduct by law.” [4] To change this situation, the Chinese government recently announced that it will invest a total of $1.2 billion in the next three to five years, or $120 million to $204 million annually, to improve the technical and personnel infrastructure for drug safety regulation [41]. By comparison, the annual budget of the U.S. FDA has been about $2 billion in each of the past few years [42]. The goal in China is that within five years, 90% of provincial and 60% of municipal drug safety control departments will be able to conduct full-scale drug safety testing [41].

In addition to financial constraints, the decentralized structure of the Chinese regulatory system remains another challenge to the quality of enforcement. While provincial drug departments have full jurisdiction over municipal and local drug departments, the SFDA shares with provincial governments the authority to oversee provincial drug departments [1]. Provincial drug departments, which receive substantial funding from the provincial governments, often choose to enforce SFDA regulations selectively to promote local developmental, employment or political objectives [4]. Because cracking down on drug safety often entails loss of tax revenue and employment opportunities in a province, provincial drug departments seem to apply looser standards for regulation enforcement. For example, it was reported that the SFDA approved only 45 applications for manufacturing establishments during the three years from 1998 to 2001. However, after the approval authority was temporarily delegated to provincial departments, 70 new establishments were approved in the first six months of 2003 alone [43].

Despite the weak, uneven and inconsistent enforcement across provinces, the government is reluctant to create an entirely centralized drug safety regulation system. Perhaps it fears such a system would further open the door for corruption and other illegal activities without necessarily improving the quality of regulation enforcement [44]. Such precaution is
understandable given that former SFDA Head Zheng Xiaoyu was found guilty of taking bribes from the pharmaceutical industry [20]. It is therefore unclear whether and how the central-provincial tension in China’s drug safety regulation will evolve. The most likely scenario seems to be that a decentralized structure will continue for many years.

The Scope of Enforcement Need

China’s drug safety enforcement task is more difficult by a pharmaceutical industry that has more than 6,000 manufacturers, 13,000 distributors, 34,000 franchise retailers, and 554,000 rural drug supply outlets [1]. By contrast, the U.S. pharmaceutical industry, which is significantly larger by sales value, consists of only 1,286 manufacturers, 50 distributors and 55,000 retailers [45, 46]. The sheer number of firms that need to be overseen makes it impossible for the SFDA to enforce its regulations in an effective and consistent manner. The sales revenue of the top 10 Chinese drug manufacturers account for only 10% of China’s pharmaceutical sales, compared to the top 10 international firms, which account for about 60% of U.S. pharmaceutical sales [10, 46]. Small producers often operate at a very low profit margin with few specialized quality control staff, meaning few of the tests needed to ensure product safety are ever performed. Many producers see government oversight as a financial burden and spend significant resources trying to outwit and avoid the system, rather than “buying in” and focusing their resources on improved compliance with GMP standards.

A large and decentralized distribution structure only adds to the difficulty. In 2005 the combined market share of the top three Chinese pharmaceutical distributors amounted to about 25% of the industry’s total sales, far less than the combined market share of more than 90% among the top three pharmaceutical distributors in the U.S. [10, 46]. Many of these small distributors have neither the scale to automate nor much expertise in distribution. Furthermore, this lack of scale means that manufacturers seeking to distribute their products nationally need to use multiple distributors [47]. The need to use multiple distributors negatively affects product quality because product traceability is hard to guarantee, and when problems arise, product recalls can be extremely difficult to manage. In addition, small
distributors usually lack sophisticated skills and equipment to identify counterfeit and substandard drugs. Some even find it profitable to collude with counterfeit drug makers.

Both the manufacturing and distribution industries will likely consolidate in the future. According to a recent report by PriceWaterHouseCoopers, international and domestic investors have started a strong wave of merge and acquisition (M & A) in China’s pharmaceutical sector. The total pharmaceutical M&A deal volumes increased from around $30 million per year prior in 2006 to about $100 million per year after 2006 [47]. Besides increased investment, declining profit margins are another catalyst for consolidation. NDRC has issued nine pricing policies to reduce drug prices since 2000 [10]. As a result, the average profit margins for drug manufacturers and distributors have reportedly decreased substantially [48]. Consolidation will increase to a certain extent incentives for large manufacturers and distributors to improve product quality as well as their ability to do so. However, regulators at both the SFDA and NDRC still need to leverage policy tools they have to facilitate faster consolidation and encourage bigger firms to be more responsible players.

5.2. Barriers and Promise for a Safety-Inducing Market Environment

Market Rewards for Safer Drugs

In some countries, market share and profitability associated with product quality and/or brand recognition often provides strong incentives for private firms to invest in their product quality. China’s health care market conditions, however, do not guarantee economic rewards for safer drugs. Effective reputational incentives rely on consumers and physicians to have reliable information about the safety performance of drugs and drug manufacturers. This is not the case in China. Unlike in the U.S. where the FDA-maintained MedWatch program is dedicated to informing and educating consumers about various drug safety issues, the Chinese SFDA has yet established any comprehensive program to systematically collect, analyze and release drug safety information. Despite recent progress in post-marketing surveillance, most drug safety information databases are generally regarded as sensitive information and are not publicly accessible. The SFDA releases limited safety information
selectively and in most cases on an ad hoc basis [49]. Due to legal and political constraints, China also lacks powerful consumer groups, such as the Public Citizen in the U.S., that advocate drug safety on behalf of consumers and educate consumers about safe and unsafe drugs [50].

The Chinese health care financing system only adds to the problem of lack of market incentives for safer drugs. In China, public hospitals account for 80% of all retail pharmaceutical sales [51]. Due to a large reduction in governmental funding, hospitals derive more than half of their revenue from a 15% markup they are allowed to charge on their drug purchase procurement prices [10]. Because most Chinese pharmaceutical manufacturers are small firms producing largely the same set of “me-too” drugs sold at prices capped by NDRC, hospitals have gained a dominant position in the market place and often demand deep “rebates” from manufacturers [52]. To afford competitive rebates to hospitals and remain financially viable, manufacturers are in turn forced to cut production costs, which often leads to lower quality standards.

Another effect of the 15% markup rule is hospitals and doctors prefer the so-called “new” drugs because they are not subject to NDRC price caps and thus are sold at higher prices [53]. This has encouraged drug makers to frequently change the form, packaging and dosage of their drugs to be qualified for “new” drug status [13]. According to a study by Peking University Guanghua Graduate School of Management, nearly 60% of the 449 generic drugs procured by one Beijing Hospital during 2004-2006 had some type of change in packaging, form or dosage [54]. Such high frequency of changes further increases the risk of introducing new quality problems and ADRs because it makes it difficult for physicians and patients to keep abreast of the many subtle, but sometimes important differences between “new” and “old” versions of the same drug. For example, ADRs might occur if patients do not recognize that the new version is more potent than the old version.

46 For example, the SFDA releases drug market quality inspection results quarterly or bi-annually. However, in most cases little information is given about how the samples were selected and what tests were applied. The SFDA also releases ADRs warnings on an ad hoc basis. But the national ADRs database, unlike in the U.S. that is publicly accessible, can be only accessed by authorized personnel at the National ADRs Monitoring Center. GMP inspection results are generally not available unless a manufacturer is revoked of its GMP certification. More information about what information is and what information is not publicly available can be found at the SFDA website (www.sfda.gov.cn) in Chinese.
In January 2009, China’s Ministry of Health proposed a plan to replace the 15% markup rule with a fixed service fee [55]. Hospitals would earn a fixed and independent service fee for each prescription they dispense, thus hopefully losing their interest in dispensing high-priced drugs, choosing instead to make prescribing decisions based on a drug’s cost-effectiveness. Meanwhile, the SFDA also narrowed the definition of “new” drug to exclude those that only include changes in form, packaging or dosage [22]. A different, but also encouraging new development is the fact that foreign firms have become increasingly influential in advocating a differential pricing policy for high quality drugs. The Research & Development Pharmaceutical Association (PDPAC), which represents dozens of international R&D-based pharmaceutical firms, has provided substantial advice for the SFDA and NDRC by sharing their expertise in international practices and business know-how [55]. Preferential pricing policy is currently being pilot tested in Guangdong province [56]. It is hoped that if successful, such policy will eventually be implemented nationwide.

Civil Penalties for Unsafe Drugs

In many developed countries, product liability laws entitle consumers to bring private lawsuits against firms that produce defective drugs. Potential litigation costs associated with settlements and damage awards often amount to millions of dollars and sometimes billions of dollars and serve as a strong deterrent – in addition to government sanctions – that incentivizes firms not to produce unsafe drugs [57]. In the United States, pharmaceutical product liability litigation involving drugs such as the diet pills Phen-fen and the nonsteroidal anti-inflammatory drug Vioxx has resulted in some of the World’s most expensive litigation events [58, 59].

In China, the product liability system remains largely undeveloped. The Chinese Consumer Protection Law entitles consumers who suffered personal or financial injuries from counterfeit or substandard products the right to sue the manufacturer or distributor. However, the total compensation for consumers is capped at two times the company’s illegal earnings [60]. In cases where there are no illegal earnings, the firm is subject to an administrative fine
of up to RMB 10,000 (about $1,500). Compared to the U.S. where pharmaceutical litigation costs to manufacturers can amount to billions of dollars, the Chinese civil penalties for defective drugs are almost trivial and are unlikely to be large enough to deter drug makers from engaging in substandard production. In addition, the Product Quality Law explicitly states that firms are not responsible from any harm or injury resulting from products that are manufactured according to national standards (a concept that is often called “regulatory preemption” in the U.S.) [61]. This Clause thus excludes victims of ADRs from pursuing compensation through the legal system because by definition ADRs relate to drugs that are manufactured according to regulatory standards set forth by SFDA [62].

In a recent encouraging development, the National People’s Congress (NPC) is currently drafting China’s first Tort Liability Law [63]. Among other things, the draft Law entitles victims and/or estates of product-related injuries to seek compensation from manufacturers, distributors or retailers of the product. In addition, manufacturers, distributors and retailers of defective products are subject to punitive damages if they are proven to have engaged in manufacturing or selling the product despite knowing that it is defective. However, the current draft still largely leaves out the issue of providing legal foundation for ADR victims to seek compensation from drug manufacturers. In March 2009, 37 NPC and People’s Political Consultative Conference Representatives submitted a petition to NPC’s Standing Committee, requesting the enactment of a National Drug Safety Law [64]. The petition suggests that China should introduce a public ADR victim compensation system to compensate victims of unsafe drugs. Hopefully these ongoing legal developments will gradually improve the incentives for drug manufacturers and distributors to improve product safety.

Section 6: Concluding Comments

Deadly pharmaceutical incidents involving sulfanilamide and thalidomide in the early and middle twentieth century pushed the United States to drastically expand and improve

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47 The National People’s Congress (NPC) is China’s highest legislative body. The NPC General Office has the most important authority in deciding the agenda of lawmaking in China. The People’s Political Consultative Conference serves an advisory body to NPC but does not have any formal legislative authority.
regulation over pharmaceutical products [65]. Today, the U.S. has one of the safest drug markets and the world’s largest and most innovative pharmaceutical industry. From this perspective, recent catastrophic events related to Chinese pharmaceutical products should be viewed as both a challenge to and an opportunity of Chinese policymakers. While high-profile executions and new laws will not drastically reduce drug-related injuries, increased enforcement and the education of consumers can accomplish much. Since SFDA cannot be omnipresent, public enforcement activities are only part of the solution. Policymakers should encourage self-regulation within the supply chain by leveraging a broader set of policy tools, such as new drug approval, GMP enforcement and pharmaceutical pricing policy, to incentivize the production, distribution and prescription of high quality products. Despite SFDA’s recent reform measures, strategic problems remain to be resolved. The modernization of China’s drug safety system, however, responds to a real and lasting grassroots demand for safer medicines by the increasingly vocal and powerful Chinese consumers. As the Chinese population becomes more affluent, such demands will only grow. It is therefore likely, if not inevitable that Chinese pharmaceutical products will improve over time. The questions are when and how such improvements in quality and safety will occur and the extent to which overall safety is improved.

References


# Appendix A: List of Interviews Conducted

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<tr>
<th>Time</th>
<th>Location</th>
<th>Interviewee</th>
<th>Interview content</th>
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<tr>
<td>Sept.2, 2009</td>
<td>Beijing</td>
<td>Deputy director of one municipal drug department in Beijing</td>
<td>GMP standards and enforcement, market quality inspection.</td>
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<tr>
<td>Sept.3, 2009</td>
<td>Beijing</td>
<td>Deputy director of one municipal ADRs monitoring center in Beijing</td>
<td>Post-marketing surveillance, ADRs monitoring, and drug recalls</td>
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<tr>
<td>Sept.3, 2009</td>
<td>Beijing</td>
<td>Senior analyst, Center for Drug Evaluation, SFDA</td>
<td>New drug approval, SFDA organization reform</td>
</tr>
<tr>
<td>Sept.4, 2009</td>
<td>Beijing</td>
<td>Senior researcher, Center for Drug Evaluation, SFDA</td>
<td>New drug approval, SFDA organization reform</td>
</tr>
<tr>
<td>Sept.6, 2009</td>
<td>Beijing</td>
<td>Senior director, Department of Policy &amp; Regulations, SFDA</td>
<td>New drug approval, GMP standards, post-marketing surveillance and other regulations</td>
</tr>
<tr>
<td>Sept.7, 2009</td>
<td>Shanghai</td>
<td>Health policy analyst, Ministry of Labor and Social Security, People’s Republic of China</td>
<td>China’s health care reform and pharmaceutical pricing policy</td>
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