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The Role of Government Reimbursement in Drug Shortages

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ABSTRACT

Beginning in the mid-2000s, the incidence of drug shortages rose, especially for generic injectable drugs such as anesthetics and chemotherapy treatments. We examine whether reimbursement changes contributed to the shortages, focusing on a reduction in Medicare Part B reimbursement to providers for drugs. We hypothesize that lower reimbursement put downward pressure on manufacturers' prices which reduced manufacturers' incentives to invest in capacity, reliability, and new launches. We show that, after the policy change, shortages rose more for drugs with (i) higher shares of patients insured by Medicare, (ii) greater decreases in provider reimbursement, and (iii) greater decreases in manufacturer prices.

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Beginning in the mid-2000s, the incidence of drug shortages rose, especially for generic injectable drugs (Figure 1). Examples include drugs used in chemotherapy, antibiotics and anesthesia, as well as injectable electrolytes and vitamins. Shortages cause doctors and patients to seek alternatives that are unfamiliar or inferior. When substitutes are unacceptable, doctors and patients delay or forego treatment.[1] Most of the drugs that experienced shortages were off-patent and had previously been readily available.[2]

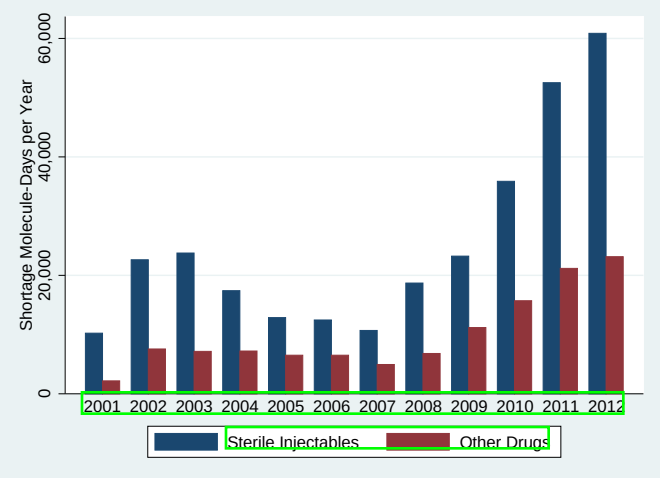

Figure 1: *Shortage days per year across all drugs. Source: University of Utah Drug Information Service*

We investigate how declining reimbursement affected the rise of shortages of sterile injectable drugs in the United States. One such change was the Medicare Modernization Act (MMA) which reduced Medicare reimbursement to the health care providers who administer these drugs.[3] We begin by specifying a theoretical model of how reimbursement policy and market size influence shortages. Our model implies that the decision by manufacturers to invest in reliability and quality depends on the expected returns.[4] If the returns are sufficiently high, then manufacturers will

[1] Metzger, Billett and Link (2012) provide clinical evidence that a commonly used substitute (cyclophosphamide) used because of shortages of mechlorethamine resulted in higher relapse rates in patients with pediatric Hodgkin's lymphoma. The American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the American Society of Anesthesiologists (ASA) have all separately detailed how drug shortages result in worse patient outcomes, higher medical care costs, and delays in clinical trials for new therapies (American Society of Clinical Oncology (2011), American Society of Hematology (2011), American Society of Anesthesiologists (2010)).

[2] See Kaakeh et al. (2011) regarding the incidence of shortages. See Panel (2009); Rosoff et al. (2012) regarding guidelines for dealing with shortages. See working papers by Conti and Berndt (2013) and Ridley, Bei and Liebman (2016) regarding shortages of cancer drugs and vaccines, respectively.

[3] Duggan and Scott Morton (2010) examine the effect of the MMA on prices in the retail market. Furthermore, Jacobson et al. (2010) examine the effect of the MMA on treatment patterns by oncologists.

[4] See also Woodcock and Wosinska (2012)

double-source ingredients, perform monitoring and maintenance on manufacturing lines, and build newer or more robust manufacturing lines. These actions can reduce the likelihood of shortages.

Consistent with the theoretical model, the empirical results suggest supply-side responses to decreasing margins. We begin by showing that drugs which had greater exposure to the policy change experienced greater increases in shortages. Exposure to the policy change is measured using the Medicare market share (MMS) – the fraction of a drug's revenue that comes from Medicare fee for service patients. This metric is similar to the Medicare market share measure used by Duggan and Scott Morton (2010) who study the effect of introducing Medicare Part D. Then, to explore our theorized mechanisms by which the policy change could lead to more shortages, we test comparative statics from the theoretical model. In particular, we show that drugs for which reimbursements fell by more after the policy change had greater increases in shortages. These results hold whether measuring reimbursement from Medicare to health providers (which was directly affected by the policy, but an indirect measure of manufacturer profitability) or a manufacturers' average revenue per dose (which was indirectly affect by the policy, but a direct measure of manufacturer profitability).

These relationships are quantitatively important. We estimate that a sterile injectable drug which has 10% less Medicare market share would have .66 fewer expected shortages days per year after the policy change, from a mean of 60. Likewise, a 10% drop in reimbursements to providers would increase the number of expected shortage days by 2.8 per year. The median drop in reimbursement from Medicare to providers for generic sterile injectable drugs after the policy change is roughly 50%.

1 Background

The pharmaceutical industry is highly regulated. A manufacturer must receive approval by the US Food and Drug Administration (FDA) before being allowed to produce a generic pharmaceutical. To be approved, the manufacturer must persuade the FDA that its generic drug is pharmaceutically equivalent to the branded drug and that the manufacturing process follows good manufacturing practices including ensuring sterility for injectable dosage forms (Scott Morton, 1999). Entry into branded drugs is also highly regulated, requiring a new molecule to demonstrate efficacy and safety compared to a placebo.

Sterile injectable drugs are typically administered in a clinical setting, such as a physician's office or in a hospital. In the U.S. a typical generic sterile injectable drug is produced by three to four of the seven big generic injectable manufacturers.[5] Sterility is critical for injectable drugs because they are administered intravenously, intramuscularly, or subcutaneously rather than passing through the gastrointestinal tract. Manufacturing lines can be contaminated by bacteria, fungus, or mold which causes delays to clean up the problem. In some cases, remediation is so costly relative to expected profit that the manufacturer stops producing the drug. Shortages might also occur due to disruptions to supplies of active pharmaceutical ingredients. Once one manufacturer stops producing, it falls to the other manufacturers to make up the supply difference. However, the other manufacturers might not find it profitable to produce more units of the drug, or might not be licensed to produce more of the drug, or might have been affected by the same supply shock as the other manufacturer. According to our IMS Health data sample which we detail later, injectable drugs totaled $83.3 billion dollars and 3.7 billion units in 2010.

The supply chain for a typical sterile injectable drug is illustrated in Figure 2. Consider a Medicare-eligible patient being treated for cancer. She visits her provider who administers a drug through injection or infusion. The provider paid the price of the drug to a manufacturer (through a wholesaler). The provider is reimbursed by Medicare for the drug. The difference between the amount that Medicare reimburses for the drug and the manufacturer's price is the gross margin for the provider.[6] Henceforth, "manufacturer's price" will refer to a payment from a provider to a manufacturer (through a wholesaler), while "reimbursement" will refer to a payment from Medicare or a private insurer to a provider.

1.1 Reimbursement Changes

Medicare provides health insurance for seniors and the disabled. Medicare covers hospitals and hospice (Part A), as well as physician visits and outpatient services (Part B). Under Part B, physicians are reimbursed when they administer a drug (often a sterile injectable). Until 2005, Medicare Part B reimbursed providers for drugs based on Average Wholesale Price (AWP). However, AWP was a list price, not an actual average price. According to the Medicare Payment Advisory Com-

[5] APP-Fresenius, Bedford-Ben Venue, Daiichi Sankyo, Hospira, Sandoz, Teva, and West-Ward. Several of these manufacturers, as well as smaller manufacturers, experienced shortages.

[6] Berndt (2002) describe the economics of the pharmaceutical industry. U.S. Department of Health and Human Services (2011) provides more detail on the sterile injectable portion of the industry.

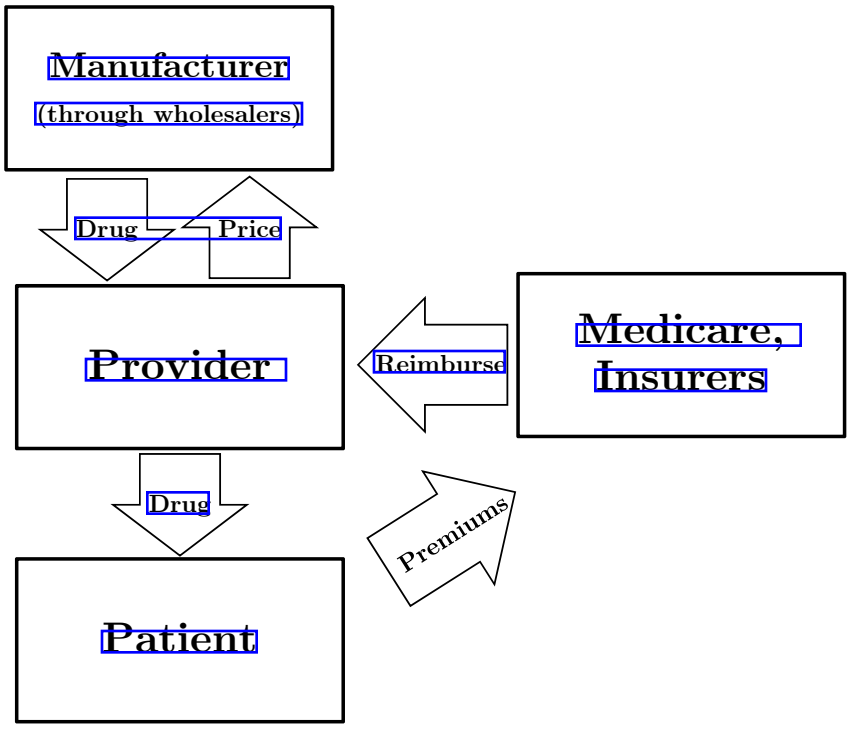

Figure 2: A provider purchases a drug from a manufacturer (through a wholesaler), then administers the drug to a patient. Medicare or a private insurer reimburses the provider for the drug.

mission (2003): "[AWP] does not correspond to any transaction price... AWP has never been defined by statute or regulation. Individual AWPs are compiled in compendia like the Red Book and First Databank". As such, the AWP was often substantially higher than the actual transaction price. Medicare Payment Advisory Commission (2003) cited some dramatic examples: Vincasar, a chemotherapy drug, had an AWP of $740, while being sold to physicians for $7.50.[7] Berndt (2005) provides a detailed history of AWP. By raising AWP, manufacturers could raise the profitability of providers that chose their drug. However, the threat of litigation and new regulation probably disciplined AWP.

In 2003, the Medicare Modernization Act (MMA) (officially known as the Medicare Prescription Drug Improvement and Modernization Act of 2003) created the retail drug benefit known as Medicare Part D and changed reimbursement under Medicare Part B. In 2004, MMA changed Medicare reimbursement from the previously used 95% of AWP to 85% of AWP. Starting January 1, 2005, Medicare began to reimburse these drugs at 106% of the previous two quarter's Average Sales Price (ASP). The ASP is the volume-weighted average price across all manufacturers of a given drug to all buyers from two quarters prior. The ASP captures actual transaction prices, including most discounts and rebates. A study by the Office of Inspector General found that the median percentage difference between AWP and ASP was 50% (Office of Inspector General, 2005). The change resulted in decreases on the order of 50% of reimbursements for these drugs to providers as seen in Figure 3. Furthermore the policy change clearly affected the level of reimbursements paid by Medicare as shown in Figure 4. There is a clear drop in revenue paid by Medicare in 2005, followed by below private growth in Medicare reimbursements. The ASP regime is not a government price control, but rather cost-based reimbursement, however it resulted in much less generous reimbursements than the previous AWP regime.[8]

The reimbursement change only directly affected Medicare fee-for-service. Private insurance and Medicare Advantage, which is administered by private insurers, were not directly affected. Enrollment in Medicare Advantage grew during the sample period from 13 percent of Medicare

[7] AWP was jokingly referred to as "Ain't What's Paid" (Mullen, 2007).

[8] The fact that ASP is based on two quarters previous introduces some rigidity into the price mechanism which likely doesn't help alleviate shortages. However, ASPs frequently rise by more than 6% from quarter to quarter in the data, so we conclude that this aspect of the switch to ASP is second order compared to the decrease in the realized levels of reimbursements.

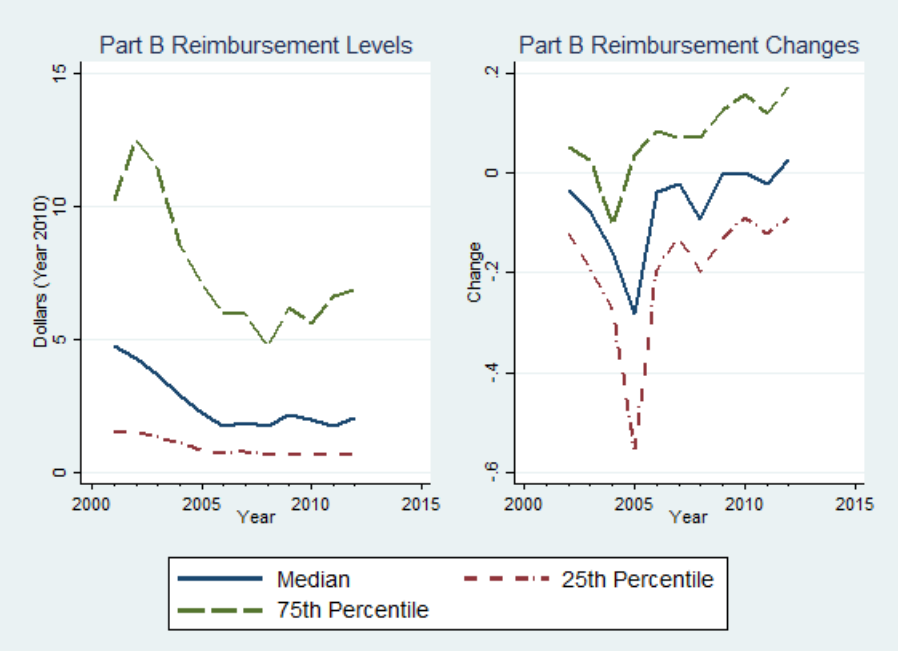

Figure 3: Reimbursement levels and changes for Medicare drugs. All drugs in this sample are off patent. The left panel is the distribution of the reimburse level for Medicare Part B. The right panel is the distribution of reimbursement changes. Each year, the reimbursement change is calculated as the reimbursement in year t minus the price in year $t-1$, divided by the price in year $t-1$, for each drug. The graph shows the percentiles of those values. All percentiles are calculated without weights across drugs.

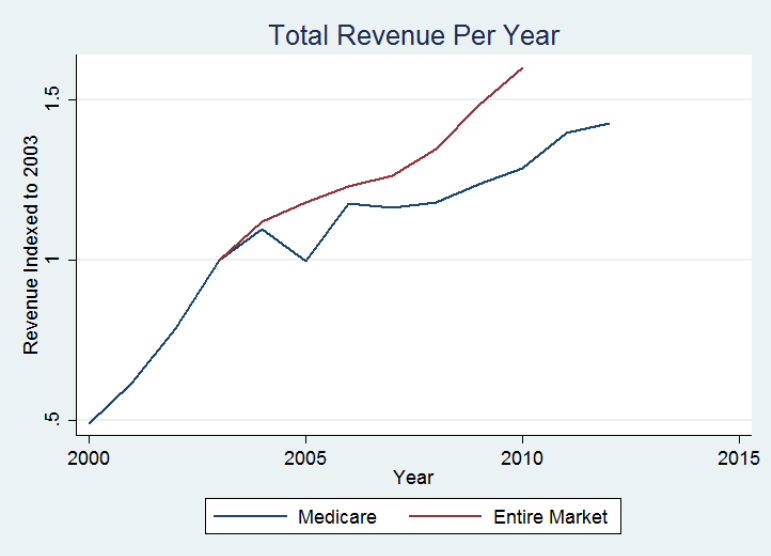

Figure 4: Blue line is total revenue of reimbursement for Medicare Part B drugs. This is the entire sample of HCPCS codes starting with J in the Part B summary files. Reimbursements have been indexed to 2003. The number of drugs in sample is allowed to vary over time. The red line is revenue for the drugs in the IMS data which are in our sample.

enrollees in 2005 to 27 percent in 2012. However, it is quite common for private insurers to mimic Medicare reimbursement, albeit with a lag (Clemens and Gottlieb, 2013). Indeed, in 2007, 21% of surveyed private payers planned to mimic ASP, while 76% intended to use rates above ASP or not use ASP (Mullen, 2007). In 2012, seven years after the change to ASP by Medicare, private insurers were using ASP for 55% of patients, according to a survey (Magellan Rx Management, 2013). Private insurers were somewhat more generous than Medicare. In 2012, the average private insurance markup over ASP was 18% (Academy of Managed Care Pharmacy, 2013, p.48). Hence, while the change from AWP to ASP was immediate for the Medicare population, it was somewhat more gradual for privately insured patients. Nevertheless, we can think of it as being caused by government policy, because private insurers typically mimic Medicare. Enrollment in Medicare Advantage grew in our sample period which would create a counter-vailing effect except that private insurers gradually followed the lead of Medicare to ASP pricing.

Another policy affected reimbursement during the sample period. The Medicaid 340b program requires that drug manufacturers offer discounts to outpatient facilities that can be classified as "safety-net providers" for low-income patients. The number of drugs purchased through 340b covered entities grew during the period. Because these drugs are offered at a discount, the growth implies lower revenue for drug manufacturers.[9] While our estimates do not isolate the effect of reduced incentives because of 340b, the mechanism at work – reduced incentives because of policies that lower payments to manufacturers – is the same. However, drug purchases under the 340B Program account for about 2 percent of all U.S. drug purchases (U.S. Department of Health and Human Services, 2013, 311).

1.2 Surplus for Providers and Manufacturers

Because of the elevated reimbursement levels, prior to the policy change, both providers and manufacturers could capture (short-run) surplus. For example, as much as half of an oncologists' income may have come from the surplus on drugs. Likewise, branded manufacturers charged

[9] Occasionally, large price increases for generic drugs make the news. Price increases tend to occur when manufacturers have market power due to exits or acquisitions. Our model (section 2) predicts higher generic prices when there are fewer manufacturers. However, these cases of large price increases for generics are rare. According to Janine Burkett of pharmacy benefits manager Express Scripts, "Price inflation among a few generic drugs has been in the news lately," but the "Express Scripts Prescription Price Index shows that, since 2008, the average price of brand drugs has almost doubled, while the average price of generic drugs has been cut roughly in half" (Burkett, 2014).

prices considerably higher than marginal costs. Even generic manufacturers can charge prices above marginal costs if fixed costs are large (some sterile injectable manufacturing requires costly facilities), products are not identical (due to reputation, availability, and relationships), or long-run equilibrium has not been reached.

MMA caused providers to be reimbursed less. Furthermore, the reimbursement change compressed the scope of price differentiation for manufacturers. With Medicare reimbursing at a 6 percent markup on average price, providers that paid a 7 percent markup on average price would lose money with each purchase. Hence, both manufacturers and providers likely lost surplus. This is consistent with previous research on vertical relationships suggesting that large firms on each side of the market share the surplus (Crawford and Yurukoglu, 2012; Grennan, 2013; Ho and Lee, 2015). Through this channel, the decreased reimbursements to providers would reduced the prices manufacturer's receive as well. We investigate the relationship between provider reimbursement and manufacturer price.

2 Theory

We use a model of entry and capacity choice with supply uncertainty to illustrate the change in production incentives and underlying welfare economics associated with changing Medicare reimbursement. This class of models has been studied by Carlton (1978), Deneckere and Peck (1995), and Dana (2001) amongst others. We consider two regimes: list-price reimbursement (AWP) and cost reimbursement (ASP). The AWP regime features reimbursement at a list price that is higher than what would normally be the acquisition price of the drug. The ASP regime features reimbursement based on costs to the provider.[10]

Manufacturers, denoted by i, simultaneously choose capacity levels k_i to produce an identical medicine. After choosing capacities, each manufacturer is hit by a shock ϵ_i which jointly follow a distribution whose CDF is $G(\vec{\epsilon})$. Manufacturer i's new capacity is $k_i\epsilon_i$.

There is a mass of size M of patients which are all willing to pay up to p_{max} for the medicine. Of those, M_{gov} are insured by Medicare. Under cost based reimbursement (ASP), if the total

[10] ASP is therefore not a regulated price. However, because ASP is based on data from two quarter previous, it does introduce some frictions into the flexibility of prices if health providers are unwilling to take a loss on individual transactions in some quarters.

capacity in the market after the shocks is less than the market size M, then the market price of the medicine is equal to p_{max}. If the total installed capacity is greater than the market size M, then the price of the good is zero.

$$p_{ASP}(\vec{k}, \vec{\epsilon}, N, M) = \begin{cases} p_{max}, & \sum_{i=1}^{N} k_i \epsilon_i < M \\ 0, & \sum_{i=1}^{N} k_i \epsilon_i \geq M \end{cases}$$

Under AWP reimbursement, the government which reimburses hospitals at p_{max} no matter what the price the hospital purchased the medicine at when they serve Medicare patients.[11] The government purchases up to M_{gov} units at p_{max} no matter what total industry capacity turns out to be. Some fraction γ of that reimbursement rate will go to manufacturers. $\gamma \in [0, 1]$ represents a bargaining power parameter which is assumed to be the same across manufacturers.

$$p_{AWP}(\vec{k}, \vec{\epsilon}, N, M, M_{gov}, \gamma) = \begin{cases} p_{max}, & \sum_{i=1}^{N} k_i \epsilon_i < M \\ \gamma p_{max}, & \sum_{i=1}^{N} k_i \epsilon_i \geq M, \text{Medicare} \\ 0 & \sum_{i=1}^{N} k_i \epsilon_i \geq M, \text{Non} - \text{Medicare} \end{cases}$$

Under ASP, manufacturer i solves:

$$\max_{k_i \geq 0} E_{\epsilon}[p_{ASP}(\vec{k}, \epsilon) k_i \epsilon_i] - c(k_i)$$

where the expectation is over the joint distribution of shocks to capacity. How much each manufacturer sells when total capacity is greater than the market size does not matter because price drops to zero when the industry is not capacity constrained and the marginal cost of production is zero up to the capacity constraint. Under AWP reimbursement, manufacturer i solves

$$\max_{k_i \geq 0} E_{\epsilon}[p_{AWP}(\vec{k}, \epsilon) Q_{i,AWP}(\vec{k}, \epsilon)] - c(k_i)$$

where Q_i is the quantity sold by manufacturer i. If total capacity is lower than market size ($\sum_i k_i \epsilon_i < M$), then this is equal to manufacturer i's capacity. If the industry has more capacity

[11] The manufacturers only receive the additional payment compared to the ASP regime on Medicare patients.

than necessary to serve the whole market, the manufacturers split the Medicare market according to what fraction of total capacity they own.[12] We assume that manufacturers produce up to capacity and do not destroy any of their product even when the industry has over-produced. One could consider variations to this game that accounted for that type of behavior. For example, once shocks are realized, new capacities could be announced publicly followed by a simultaneous move game where each manufacturer decides how much quantity to supply to the market. Depending on the realization of the shocks, a single manufacturer may be large enough to unilaterally withhold enough quantity to avoid the market price falling to zero. Borenstein, Bushnell and Wolak (2002) document this type of behavior in the California electricity generation industry. However, there will still be states of the world where this incentive does not exist, and Medicare's reimbursement under the AWP regime will affect investment incentives.

The incentive to invest in capacity is determined by integrating prices over the joint distribution of ϵ. Manufacturers must pay an entry cost F to produce and sell the good. The equilibrium number of firms is given by the maximum number of firms such that the variable profits of each firm are greater than F.

We find a symmetric Nash equilibrium to the simultaneous capacity choice sub-game. If the distribution of ϵ has no mass points, then the symmetric equilibrium capacity per firm when N firms are producing is the solution to the following equation under ASP:

$$E_\epsilon[p_{ASP}(k \otimes \mathbf{e}_N, \epsilon, N, :)\epsilon_i] - c'(k) = 0$$

where $\mathbf{e}_N$ is the $1xN$ vector of ones. Under AWP reimbursement,

$$E_\epsilon\left\{\begin{array}{ll} p_{max}\epsilon_i & \sum_{j=1}^{N} k\epsilon_i < M \\ \gamma p_{max} M_{gov} \frac{\epsilon_i(\sum_{j=1}^{N} k\epsilon_j - dk)}{(\sum_{j=1}^{N} k\epsilon_j)^2} & \sum_{j=1}^{N} k\epsilon_i \geq M \end{array}\right] - c'(k) = 0$$

We use numerical simulation to show how equilibrium quantities vary with model parameters.

When $\gamma > 0$, equilibrium capacities and average prices are higher under AWP than ASP. Shortages occur less frequently under AWP than with ASP (Figure 5). Whether total welfare is higher

[12] Because the price for non-Medicare buyers and marginal costs of production are both zero, how manufacturers split the non-Medicare quantities does not affect their profits.

or lower is ambiguous. When a firm enters the industry, it does not capture the full social value of its investment, because competition drives average price below p_{max} in some states of the world.[13] In the other direction, the government must raise the funds to pay for the AWP reimbursement, potentially distorting the decisions in some other area of the economy. Poorly designed AWP reimbursement can also lead to over-entry and over-investment in capacity.

The model's predictions for levels are not surprising. The AWP reimbursement continues to pay manufacturers for Medicare patients even when the industry over-produces. This implies higher returns to investing in capacity for manufacturers, thus more total capacity and fewer shortages. The model is useful for empirical analysis because it predicts a differential impact of the AWP reimbursement depending on features of the drug. In particular, drugs with lower fixed costs and that serve more Medicare patients will experience a greater increase in shortages moving from AWP to acquisition cost based reimbursement as in ASP.

The contracts negotiated between health providers, wholesalers, and manufacturers are more complicated than the simple model put forth here. Contracts often have non-linearities due to bundled discounts or quantity discounts or other material clauses. Modeling the nexus of non-linear contracts between strategic agents would be an important advance to the maintained model. However, it is unlikely that such a model would change the result that moving from AWP to ASP reimbursement decreases incentives to invest in capacity. This is because in such models of the nexus of linear contracts in other industries (for example Crawford and Yurukoglu (2012)) the price to the upstream firm, the manufacturer in this paper, will depend strongly on the surplus created by consumption of the good and competition. Non-linearities in the contracts may reduce or sharpen this dependence, but there is no theoretical basis that they would overturn the dependence. Since prices and demand for each product determine the incentives to invest in capacity, the simple model here captures the first-order determinants of these investment decisions.

3 Data

An observation is a drug and year. We refer to a drug as an active ingredient or combination of active ingredients. For example, the nutritional product Multiple Vitamins for Infusion (MVI)

[13] In this model, conditional on having the socially optimal number of firms, the capacity choices are socially optimal. This is because price rises to p_{max} immediately in a shortage. With less flexible pricing or competitive pressures in shortage states, capacity investment could also be too low under ASP.

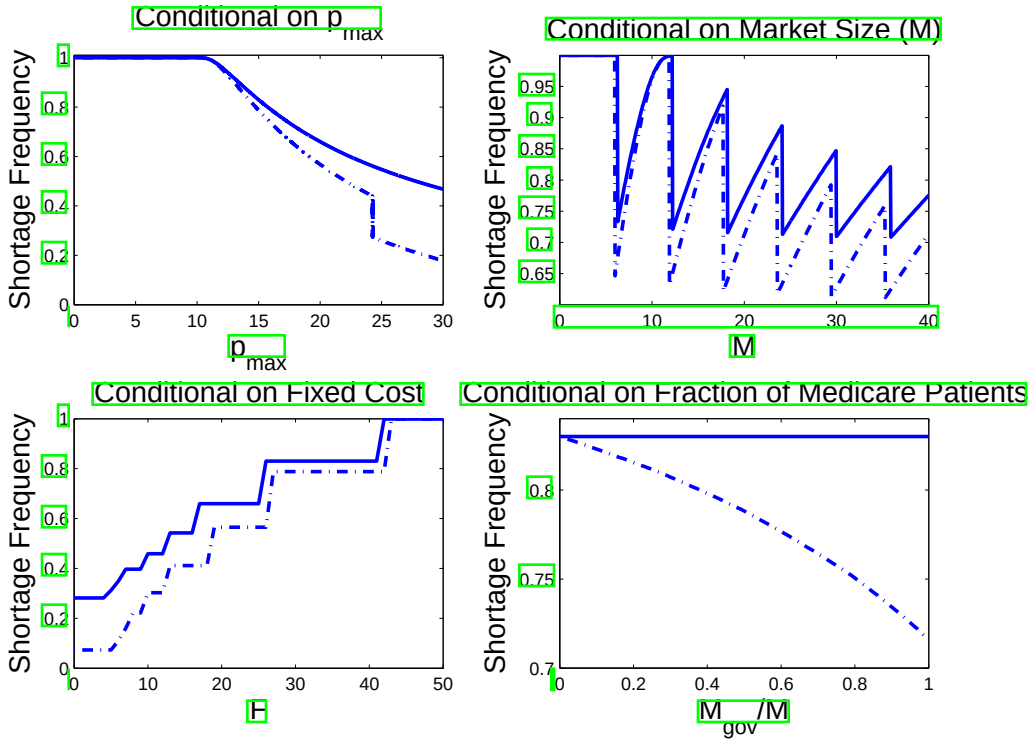

Figure 5: Model's predictions of shortage frequency as functions of model parameters. The solid lines are predictions for the cost-based ASP reimbursement regime. The dashed-dotted lines are predictions under the AWP reimbursement regime. Increasing p_{max} makes capacity investment more desirable and can induce entry. Raising market size has two effects: (1) It makes entry more desirable as there are more consumers for the medicine. However, it also means that the industry needs to produce more to satisfy demand which can make capacity investment less attractive depending on the shape of the cost of capacity function. When fixed costs increase, fewer firms enter. This leads to higher margins and more capacity investment in equilibrium. Finally, when the share of Medicare patients rises, capacity investment becomes more attractive in the AWP regime while it is unaffected in the ASP regime.

is a combination of active ingredients that also exist as stand-alone drugs. We only consider drugs whose route of administration is intravenous or injectable.

We use five data sources. First, we use Medicare Part B revenue and quantity data from the CMS Part B National summary files. Second, we use privately-insured outpatient hospital (analogous to Medicare Part B) revenue and quantity data from the MarketScan Commercial Claims and Encounters Database. Third, we have total US drug revenue and quantity data across all payers (Medicare, Medicaid, private insurance) and settings (physicians, hospitals, retail) from IMS Health. Fourth, we have shortage data by molecule and year from the University of Utah Drug Information Service. Fifth, we have approval dates and the number of manufacturers per molecule from FDA Orange Book.

First, we use Medicare reimbursements and services given by the Part B national summary files. The key variables are the total reimbursements by Medicare and number of services billed for a Healthcare Common Procedure Coding System (HCPCS) code and year. Providers use HCPCS codes to bill Medicare and private payers for procedures. A typical HCPCS code represents one administration of a drug. For example, the spending by Medicare to a hospital or physician's office on a lymphoma patient being treated by chemotherapy agent Doxorubicin once a month for three months would show up as three services of HCPCS code J9000. The same drug can have multiple HCPCS codes representing different dosages. We use data from 2001 to 2012 and adjust reimbursements for inflation to year 2010 dollars. CMS also provides data on the Average Sales Price (ASP) by HCPCS code by quarter from 2005 to the present. The ASP is the quantity weighted average sales price accounting for discounts and rebates in the previous two quarters. The data for Q1 2005 provide a glimpse at payments manufacturers were receiving for two quarters under the AWP based reimbursement scheme.

Second, we use MarketScan Commercial Claims and Encounters database outpatient files. These data are given at the claims-level, but we aggregate to the year and HCPCS code. The data are not nationally representative, but rather they are a convenience sample of all claims from large employers and insurance plans. The data only include enrollees who are under 65. As discussed later, we reweight the data to match the population of the commericially insured population in the U.S. We use the years 2001-2009 to estimate the total non-Medicare spending, adjusted for

inflation to year 2010 dollars, by year and HCPCS code as well.

Third, we use IMS MIDAS data for estimates of a drug's total revenue for the years 2003 to 2010. We use these data to esitmate sales to providers. These data contain all payers, including private, Medicare, Medicare Advantage, and Medicaid.

Fourth, we use shortage data from the University of Utah Drug Information Service (UUDIS) which archives shortages that were reported to the FDA or the Association of Health System Pharmacists (ASHP) by providers (hospitals or pharmacists) or manufacturers. In the data, a drug shortage is defined as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent" (Fox et al., 2009). A report of a shortage leads to a response from the FDA and ASHP which usually results in recommendations for rationing drugs and alternative drugs that can be used. Manufacturers are also contacted to determine which manufacturers, if any, have emergency supplies. This suggests that the reporting of shortages is vetted by manufacturers and the FDA. Shortages are molecule and form (injectable or not) specific and are for the entire U.S. We also have information on the dates of shortage start and when they are resolved. We use shortage data from 2001 to 2012.[14]

Fifth, we use the Food and Drug Administration's Orange Book for the years 2001-2012 to record how many approved manufacturers of a drug (active ingredient and route of administration combination) exist in each year, and the number of years since the earliest approval of a manufacturer of the drug. The FDA Orange Book records each approved and active manufacturer[15] of a given drug in a given year. Because the analysis is at the drug level, we collapse the observations of a given drug into one observation per year. The Orange Book does not track biological pharmaceuticals which are made by a biological process rather than chemical synthesis (e.g. insulin). These drugs have a more complicated manufacturing process and have been subject to some shortages. Most biologicals are still on patent. This paper focuses on chemically-synthesized compounds which make up the majority of administered drugs.

[14] An alternative set of vaccine shortage data are offered by the FDA. The FDA uses a stricter definition of a shortage than the UUDIS. However, historical FDA data are not available. The UUDIS measures of shortages are widely used in the pharmaceutical literature Fox et al. (2009); Fox, Sweet and Jensen (2014).

[15] Approved products whose manufacturers no longer actively market the product are listed as "discontinued" in the Orange Book. The number of manufacturers variable we construct from the Orange Book only counts active manufacturers.

3.1 Medicare Market Share (MMS)

MMS is the fraction of a drug's revenue from Medicare Part B. We use MMS to identify which drugs will be more impacted by the Medicare reimbursement change. Hence, for MMS, cardinality is not particularly important, but ordinality is.

We use two estimates of MMS. For both measures, the numerator is Medicare Part B sales to physicians. These were the only sales directly affected by the policy change of switching to ASP pricing.[16] The two MMS measures vary according to the denominator: total drug revenue. In the first measure of MMS, the denominator is the sum of revenue for each drug from the IMS database. In the second measure of MMS, the denominator is the sum of revenues for each drug in the MarketScan database plus the revenues to Medicare Part B. The number of people in the MarketScan data rises from around five million in 2001 to 37 million in 2009. To create the MarketScan-based estimate of MMS for each year, we scale the revenue by drug as if the sample were nationally representative.[17] For example, suppose there are 10 million individuals in a given year in the MarketScan data. We scale the revenue of each drug by the US population minus the number of individuals insured by Medicare and/or Medicaid divided by 10 million.

Medicare serves seniors and those with kidney failure. Consistent with this, the drugs with the highest MMS include inhalants for chronic obstructive pulmonary disease (a progressive disease caused by smoking), Pegaptanib Sodium (for age-related macular degeneration) and Triptorelin Pamoate (for prostate cancer). Other drugs with the highest Medicare share are immunosuppressants used in kidney transplants which are covered by Medicare for all ages. The drugs with the lowest Medicare share are those used by a younger population, including Somatrem (human growth hormone for children), Glatiramer Acetate (for multiple sclerosis), two drugs which treat hyper-thyroidism, and Urofollitropin (a fertility drug).

While the data used to construct the numerator, reimbursements from Medicare Part B, are all the payments affected by the policy change, we adjust our methods to handle imperfect data in the denominator. The IMS measure is not perfect as it mixes revenues to manufacturers with

[16] The Medicare Part B data do not include Medicare Advantage payments. In 2012, Medicare Advantage accounted for 27% of all Medicare enrollees.

[17] The data vendors do not claim that the data are nationally representative of the private insurance market. However, Dunn, Liebman and Shapiro (2014) find evidence that reweighting MarketScan data improves the representativeness of the sample.

revenues from Medicare to doctors. Nonetheless, it is a measure of the relative importance of Medicare revenues to non-Medicare revenues. For example, if revenue to a manufacturer is a constant fraction of reimbursements to doctors, then this measure would be equal to the true MMS times a constant. As such, drugs which derive more of their revenue from Medicare would have relatively higher values of this variable. While not ideal for interpreting units, the first-order role of this variable is to detect differences in the change in shortages between drugs which are more or less reliant on Medicare. The MarketScan measure might have some error because it is only a convenience sample of the under-65 private insurance market and misses sales to other payers like Medicare Advantage, Medicaid, etc. and sales in other settings like retail or inpatient hospital.[18] As we discuss in section 4.1, we use an instrumental variables strategy to address this measurement error.

3.2 Sample Definition

To combine these data sources, we begin with all HCPCS codes beginning with J ("HCPCS J Codes"), which indicates drug administration,[19] in the period 2000 to 2012 that we observe in some year's Medicare Part B National Summary File. For each of the 690 observed unique HCPCS J codes,[20] we determine the relevant active ingredient(s) and route of administration by examining the HCPCS description and searching the FDA Orange Book when possible.[21] This leaves 496 unique HCPCS J codes whose active ingredient(s) and route of administration have a match in the FDA Orange Book. We keep drugs whose route of administration is "injection," leaving 396 HCPCS J codes. Some drugs have multiple dosages with different HCPCS J codes. The 396 HCPCS codes correspond to 327 drugs.

We join this set of drugs to the shortage data by year, active ingredient(s), and route of administration, keeping all unmatched observations. If an observation from the matched set of drugs with HCPCS code J does not match to any shortage observation, we record that drug as not having shortages in the period of the sample. We join these data to the collapsed FDA Orange Book by

[18] Missing sales to other settings is less of concern because most drugs get most of their revenue from one setting. For example, a drug mostly used in retail would not usually have large sales in a hospital setting.

[19] Codes J0000 - J0849 indicates "Drugs other than Chemotherapy" and Codes J8521 to J9000 indicate "Chemotherapy Drugs."

[20] The average HCPCS J code contains 15.12 10-digit National Drug Code (NDC) codes.

[21] The Orange Book does not cover biologics, vaccines, and some nutritional products that did not require FDA approval.

active ingredient(s) and route of administration and year, keeping only matched observations. In addition to the HCPCS J code drugs which don't appear in the Orange Book[22], this excludes all the FDA Orange Book approval data for drugs which are never allocated an HCPCS code beginning with J.[23] The final sample consists of 308 drugs. Of the 308 drugs in the sample, 62 are always on-patent, 120 are always off-patent, and the other 126 switch from on-patent to off during the sample period. The full list of drugs in the sample is in Appendix A.

Next, we join this set of drugs to the IMS MIDAS data by year, active ingredient(s), and route of administration. Ten drugs were dropped because their MMS was greater than 1. This leaves the sample of drugs which have a MarketScan MMS and Medicare Reimbursement information at 298. An additional two drugs do not have Medicare reimbursement associated with them. With the IMS data, because we are merging by ingredient name, there is not perfect overlap, for 42 drugs we were unable to match an IMS observation to that ingredient. This leaves the sample of drugs which have IMS MMS and payment information at 256.

Finally, we join these data to the Medicare reimbursements from the Part B National Summary File by HCPCS code and year, average ASP by HCPCS code and year[24], and private payments from MarketScan data by HCPCS code and year. There are seventeen additional active ingredient(s) and route of administration combinations which never manifest in the MarketScan data. These are nearly all on patent at some point in the sample period, and so do not affect the major results of the paper.[25]

4 Empirical Analysis

We begin by using a differences-in-differences identification strategy to show that drugs that had greater exposure to the Medicare policy change, measured using the Medicare market share (MMS), had the greatest increases in shortages (section 4.1). Ultimately, our model suggests that shortages result from reduced manufacturer's prices, which we hypothesize results from lower reimbursements to providers. We show that reduced reimbursement to providers, caused by the

[22] There are seven such HCPCS J codes. These drugs all were matched by ingredient, but the indicated route of administration does not exist in the Orange Book.

[23] These are the majority of all drugs, such as prescription tablets taken at home.

[24] Because of data availability, the matching begins in 2004.

[25] We also ran the analysis assigning this subset of drugs an MMS of 1 and a degenerate age distribution at 60. The results of the paper are not sensitive to this assignment.

policy change, is correlated with increased shortages (section 4.2). Then consistent with our prediction that reduced incentives to manufacturers would lead to more shortages, we show that lower prices to manufacturers are correlated with more shortages (section 4.3). Following the discussion of vertical markets with bargaining power on each side (section 1.2), we show that lower reimbursements to providers are correlated with lower manufacturer's prices (section 4.4).

Throughout this section the unit of analysis is a drug and year. We log Medicare market share because the observed distribution of MMS is skewed. Similarly, we log prices throughout the analysis. To reduce noise in the measure of the Medicare market share, and because the sample period for the IMS data is shorter than the whole sample, we average across years to get compute one measure for each drug.

4.1 Shortages Conditional on Medicare Market Share

First, we test the hypothesis that those drugs most affected by the ASP reimbursement, drugs which derive a large fraction of their revenues from Medicare Part B, experience larger increases in shortages. We use a difference-in-difference model where the treatment used is the Medicare (Part B) Market Share (MMS_i) of drug i and the second difference is before and after the policy change. The specification is motivated by the assertion that Medicare Market Share is a feature of the diseases that the drug treats, and is not affected by post-policy changes in the unobservable determinants of shortage days. The first set of regressions uses a binary pre and post period, where the treatment was assumed to be applied in 2005, when ASP based pricing went into effect. Formally, this is modeled as:

$$Shortage_{it} = \alpha_i + \delta_t + \beta Post_t \times log(MMS_i) + \gamma \mathbb{1}(Off\ Patent_{it}) + \epsilon_{it} \quad (1)$$

$Shortage_{it}$ is the number of shortage days in year t. α_i and δ_t are drug and year fixed effects, which control for time-invariant differences across drugs, including the main effect of $log(MMS_i)$, and a general time trend. Then, assuming parallel trends without treatment, β is the treatment effect – the extra shortage days caused by having higher MMS post-regulation. $\mathbb{1}(OffPatent_{it})$ is an indicator for whether that drug and year observation was off patent. We classify a drug as off patent

if it has been at least 15 years since the molecule was approved.[26]

As discussed in (Section 3.1) we are concerned about error in our measures of MMS. Under the assumption of classical measurement error, the coefficient on the interaction term, β, will be attenuated towards zero. We therefore employ instrumental variables to deal with the measurement error. Because we ultimately interact MMS with the ASP reimbursement dummy variable, we follow the suggestion in Procedure 21.1 of Wooldridge (2010) to first use the MarketScan based MMS estimate and the mean age of patients who receive the drug in the MarketScan database as instrumental variables for the IMS database-based MMS estimate.[27] We then interact predicted MMS with the ASP reimbursement dummy variable. This interacted value serves as the instrumental variable for the interaction of the ASP reimbursement dummy variable and the IMS MMS measure in a standard two stage least squares procedure.

We then run a number of falsification tests and robustness checks. First, if drugs with higher Medicare market shares were experiencing an increase in shortages prior to the policy change, then the coefficient estimate would be misinterpreted as evidence that the policy change had led to an increase in shortages. We assess whether such an effect exists by running the same specification as equation 1, but limiting the sample to 2001 to 2004, and considering 2003 and 2004 as a pseudo-"ASP Reimbursement" period.

In addition, we use a flexible difference-in-difference method to see whether there are pre-trend effects and observe the dynamics of the treatment effect over time. This is modeled as:

$$Shortage_{it} = \alpha_i + \delta_t + \beta_t Year_t \times log(MMS_i) + \gamma \mathbb{1}(Off\ Patent_{it}) + \epsilon_{it} \quad (2)$$

where $Year_t$ are indicators for each year, that is interacted with the MMS which is constant across years.

[26] This is consistent with Grabowski, Long and Mortimer (2014) who found that, for drugs experiencing initial generic entry between 2000 and 2012, the mean time since launch (which usually follows a few months after approval) was about 13 years with a standard deviation of about 3 years. Our results are not sensitive to varying the threshold from 15 to 12 or 18.

[27] The MarketScan data covers patients who are under 65. The logic is that if the drugs are taken by older patients in the MarketScan data, then they are more likely to be taken by Medicare patients as well.

As shown in the model, because of their lower margins, off patent drugs should be more affected by the change to ASP than on patent drugs. To test this, we interact an indicator for patent-status with an indicator for post-regulation status. Then, we interact those indicators with Medicare market share to test whether the importance of Medicare is largest for the off patent drugs. This is modeled as:

$$\begin{aligned} Shortage_{it} &= \alpha_i + \delta_t + \beta Period_t \times \mathbb{1}(Patent\ Status_{it}) \\ &+ \beta Period_t \times \mathbb{1}(Patent\ Status_{it}) \times log(MMS_i) + \epsilon_{it} \end{aligned} \tag{3}$$

where $Period_t \times \mathbb{1}(Patent\ Status_{it})$ is the cross product of period (pre and post-regulation) and patent status (on and off).

4.2 Shortages Conditional on Reimbursements to Health Providers

Previously, we discussed why declining reimbursements to providers would affect a manufacturer's profit (section 1.2). In this section, provide indirect evidence of this effect, by checking whether the reduced reimbursements to providers increase the rate of shortages. Under the assumption that a majority of the variation in price was due to the policy change (see figure 3), then most of the variation in price can be considered exogenous which allows us to use OLS. The specification we use is:

$$\begin{aligned} Shortage_{it} &= \alpha_i + \delta_t + \beta_1 log(Reimbursement\ per\ service_{it}) \\ &+ \beta_2 \mathbb{1}(Patent\ Status_{it}) + \epsilon_{it} \end{aligned} \tag{4}$$

where $Reimbursement\ per\ service_{it}$ is the mean reimbursement (revenue divided by quantity) by Medicare in year t for drug i. In practice, this should be similar to the AWP or ASP during the respective reimbursement regimes. Drugs which go into shortage experience increases in price which translate into increased Medicare reimbursements after 2005 with ASP based reimbursement. Therefore, the OLS regression will underestimate the effect of drug prices that have risen in

response to shortage. To control for this we use one-year lagged reimbursement values to control for this effect of shortages on prices.

We also condition on the patent-status ($\mathbb{1}(Patent\ Status_{it})$) since it plays important roles in the theory. Finally, α_i and δ_t are drug and time fixed effects.

One possible worry in this regression is that unobservable demand shocks are driving both prices and shortages. However, a positive demand shock would lead to higher prices and more shortages, holding supply fixed. This biases the estimates in the opposite direction of what we ultimately find, which is that higher prices are correlated with fewer shortages.

4.3 Shortages Conditional on Manufacturer's Prices

In the previous section, we analyzed changes in shortage frequency with variation in reimbursements to health care providers. While the law directly affected reimbursements to providers, our model suggests that shortages depend on manufacturers' incentives. In this section, we analyze the effect of manufacturer's prices on shortages. To do this, we use the IMS data, which measures wholesale prices. Similar to section 4.2, we regress shortages on the price manufacturers receive. We also try lagged price to control for shortages raising prices of drugs. Formally, the specification we use is:

$$\begin{aligned} Shortage_{it} &= \alpha_i + \delta_t + \beta_1 log(IMS\ price_{it}) \\ &+ \beta_2 \mathbb{1}(Patent\ Status_{it}) + \epsilon_{it} \end{aligned} \tag{5}$$

Because the Medicare market is a smaller portion of the market, overall price changes may not be solely determined by the MMA. However, as discussed above, there is evidence that private insurers followed Medicare into ASP pricing. If private insurers did this without any lag, then we could again think of price changes as exogenous. Figures 6 and 7 demonstrate the identifying variation. In particular, there were considerable price declines for the most expensive high MMS drugs, those that were most likely to have inflated AWP and where the reduced reimbursement would affect the largest share of sales by the manufacturer.

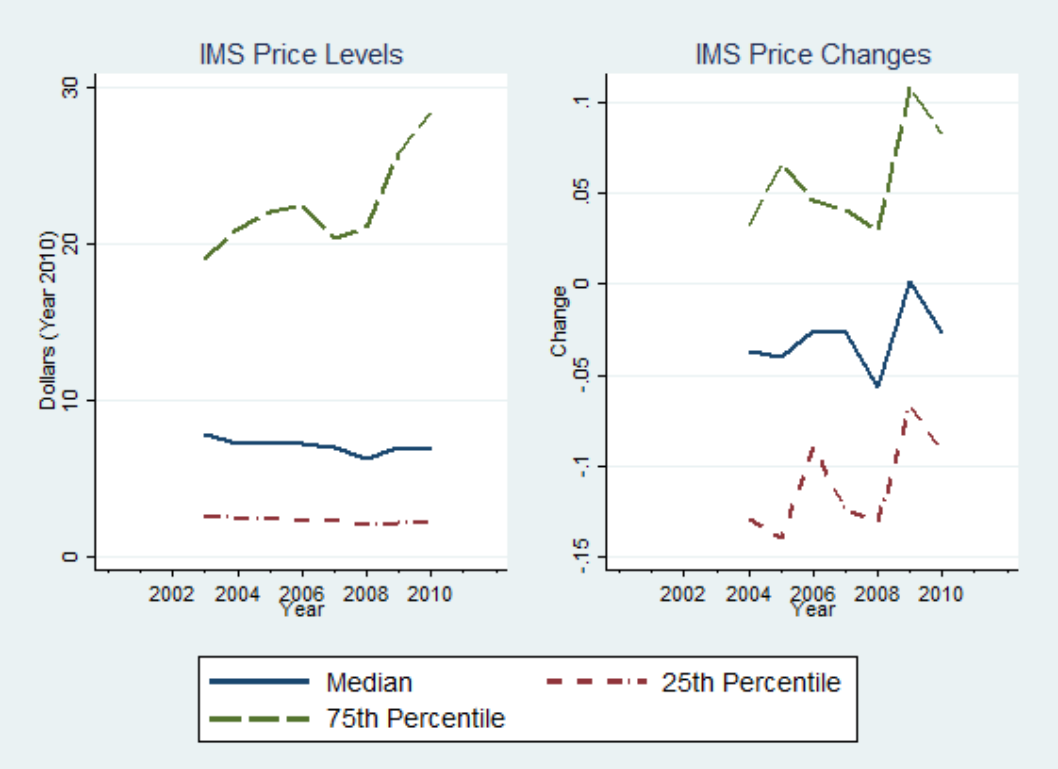

Figure 6: Price levels and changes for IMS drugs. All drugs in this sample are off patent. The left is the distribution of the price level for IMS. The right panel is the distribution of price changes for IMS. Each year, the price change is calculated as the price in year t minus the price in year $t-1$, divided by the price in year $t-1$, for each drug. The graph shows the percentiles of those values. All percentiles are calculated without weights across drugs.

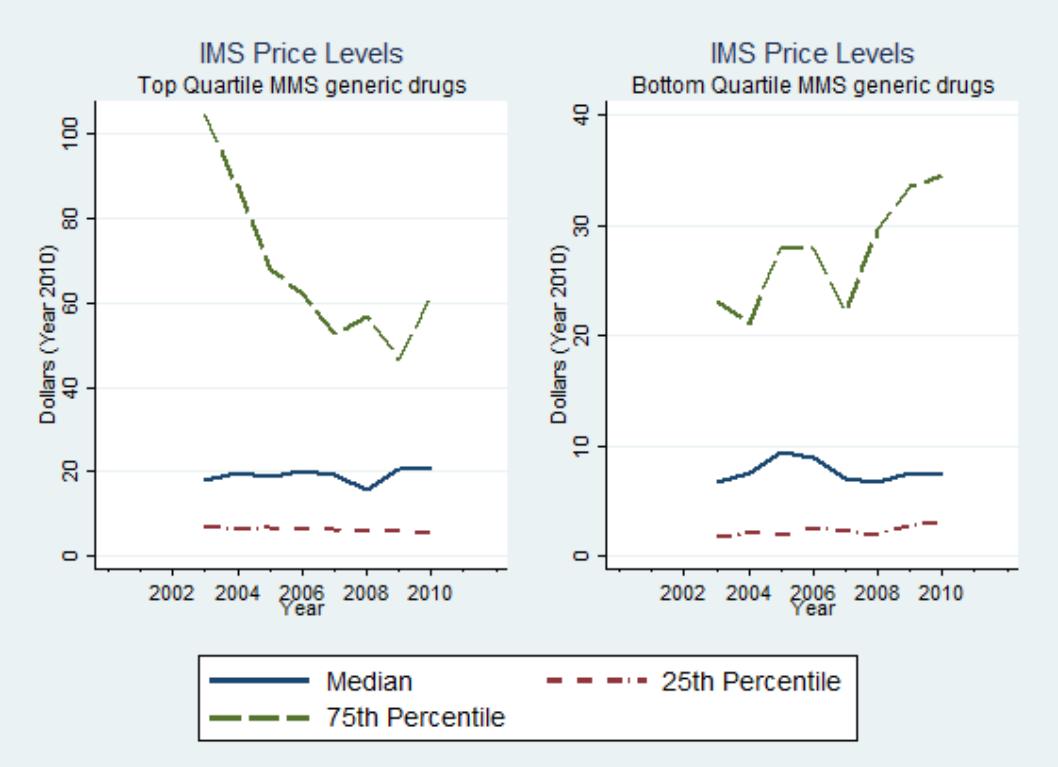

Figure 7: On the left are price levels for drugs in the top quartile of MMS, meaning used by seniors. The prices are falling for the highest price drugs targeted at seniors. On the right are price levels for the bottom quartile of MMS, meaning used by younger patients. All percentiles are calculated without weights across drugs.

4.4 Correlation in Payments to Providers and Manufacturers

As discussed in (section 1.2) the mechanism relies on the assumption that the manufacturer's prices were reduced for drugs where the reimbursement to providers was reduced. To test this assumption, we regress the Medicare reimbursement per service, a measure of reimbursement to providers, on the IMS price, a measure of manufacturer's prices. Also, to show that this effect is strongest for drugs where Medicare plays a larger role, we interact the MMS with the Medicare reimbursements. Formally, this is modelled as:

$$\begin{aligned} log(IMS\ Price_{it}) &= \beta_0 + \delta_t + \beta_1 log(Reimbursement\ per\ service_{it}) \\ &+ \beta_2 MMS_i \times log(Reimbursement\ per\ service_{it}) + \epsilon_i \end{aligned} \tag{6}$$

5 Results

The top panel of Table 1 gives summary statistics for the main sample – all drugs which we were able to merge with IMS data. Table 13 in the appendix gives summary statistics for all the drugs with Medicare reimbursement data, a sample which is used in some specifications when the IMS data are not used. There are 256 drugs in the main sample. The lower panel gives summary statistics for off and on-patent drug year observations separately. The average time that a drug is in shortage was 60 days (unconditional on being in shortage), but was 79 days and 9 days for off- and on-patent drugs, respectively. 72 percent of drug-year observations are off-patent. The average number of manufacturers for an off-patent drug is 3.54. Using the IMS data, the average MMS is 0.09 and using the MarketScan data the average MMS is 0.14. The MarketScan MMS measure is larger because it does not include spending by payers like Medicare Advantage, Medicaid or Veteran's Affairs or payments from settings like inpatient hospitals in the denominator. There are fewer values of Medicare reimbursement because we do not always observe prices for these drug-year combinations. Also, there are fewer values for the revenue per standard units because that data are only available from 2003-2010. In the MarketScan data, the mean patient age is 45.

Figures 3 and 6 gives the distribution of prices for generic drugs in Medicare and IMS, respec-

tively. For both figures, the left panel is the distribution of price levels, for example, 75 percent of Medicare drugs had prices below 10 in 2003 and below 6 in 2010. The right panel is the distribution of price changes, for example 25 percent of Medicare drugs had price declines of 50 percent in 2005 (compared to 2004), while 25 percent of drugs had declines of 25 percent in 2010 (compared to 2009). The price declines appear isolated to 2005, suggesting that they are due to the law change. Figures 8 and 9 in the appendix show the distribution for all drugs, which has similar patterns, though less pronounced.

On the other hand, IMS prices are less affected in 2005. This may be because the impact of Medicare is diluted in this market. To provide some evidence of this, Figure 7 shows the price distribution for the top and bottom quartile of Medicare market share drugs. The left panel shows prices for drugs which get the smallest share of their sales from Medicare, the right are the drugs in the top quartile. We see large, slow price declines in drugs which have a lot of Medicare sales versus those which don't. This suggests that while not all drugs are affected by the law change, those most affected were those where the Medicare population plays the largest role. This is consistent with the idea that Part B isn't a huge part of the market (Medicare is roughly 30 percent of the market and 30 percent of Medicare is in Medicare Advantage), but for drugs where it is important, overtime prices fall in all markets as other payers switch to ASP. This may help explain the lag in shortages after the law change.

5.1 Results for Shortages Conditional on Medicare Market Share

Table 2 presents the difference-and-differences relationship between shortages and Medicare market share. Columns (1) and (2) OLS and IV give the estimates without age in the instrument set. Because the specification has year indicators, we have differenced out the time-trend in the results. The OLS estimate of β is 5.7, while the IV estimate is 6.6. As expected, the IV estimate is larger due to the correction of measurement error. The results imply that an increase in the MMS from the mean of .09 to .1 leads to a 0.63 and .73 day increase in the number of shortage days, for the OLS and IV estimates, respectively. Column (3) is a robustness check where we include age and age-squared in the instrument set. Column (4) and (5) use the MarketScan MMS as the endogenous variable, where column (4) is the OLS estimate and column (5) is the IV which uses the IMS MMS as an instrument. Using the MarketScan MMS gives larger point estimates and

Table 1: Summary Statistics

	source	count	mean	sd	min	max
Shortage Days	Univ. Utah	2949	59.88	120.53	0.00	365.00
Number of Manufacturers	Orange Book	2949	2.80	2.91	0.00	25.00
MMS	IMS	2949	0.09	0.16	0.00	1.00
MMS	MarketScan	2949	0.14	0.18	0.00	0.85
Medicare Reimbursement	Part B	2544	54.92	216.32	0.01	2500.62
Mean Age	MarketScan	2949	44.91	7.48	12.83	57.39
Off Patent	Orange Book	2949	0.72	0.45	0.00	1.00
Revenue per Standard Unit	IMS	1837	208.50	584.77	0.01	12533.00
Observations		2949				

		Off Patent			On Patent		
	source	count	mean	sd	count	mean	sd
Shortage Days	Univ. Utah	2130	79.29	133.69	819	9.37	47.97
Number of Manufacturers	Orange Book	2130	3.54	3.12	819	0.88	0.32
MMS	IMS	2130	0.08	0.15	819	0.11	0.17
MMS	MarketScan	2130	0.12	0.15	819	0.19	0.23
Medicare Reimbursement	Part B	1956	32.98	122.12	588	127.88	382.26
Mean Age	MarketScan	2130	44.13	7.27	819	46.93	7.67
Off Patent	Orange Book	2130	1.00	0.00	819	0.00	0.00
Revenue per Standard Unit	IMS	1316	99.27	386.63	521	484.39	850.24
Observations		2130			819		

Summary statistics from 2001 to 2012 for the 256 drugs in the sample. MMS is Medicare Market Share.

implied magnitudes. The IV coefficient of 9.6 implies a change from .14 to .15 in MMS, leads to a 1.03 day increase in the number of shortages. These estimates show that for a number of specifications, drugs with higher Medicare market share were more likely to be in shortage after the MMA went into effect.[28]

Table 3 gives the initial first stage result, where we regress the log of IMS MMS on the instrument set. Table 4 gives the first-stage in the main regression, where the interaction of predicted MMS with the ASP reimbursement dummy serves as an instrument for log of IMS MMS interacted with the ASP reimbursement. In each table, column (1) uses the log of IMS MMS as the endogenous variable and the log of MarketScan MMS as the instrument, (2) includes age and age-squared in the instrument set and (3) uses the log of MarketScan MMS as the endogenous variable and the log of IMS MMS as the instrument. For the initial first stage, the F-statistic is well above 10, the usual rule of thumb for instrument relevance in each specification.

In Table 5, we check the impact of the definition of an off-patent drug. We vary the years since first approval we use to define a drug as off-patent from 18 years in columns (1) and (2), 12 years in columns (3) and (4), and 2 years in columns (5) and (6). Furthermore, unlike our standard definition of off-patent, we do not redefine drugs with multiple manufacturers as off-patent as well. The odd columns are OLS results while the even numbered columns are IV results. Changing the patent variable leads to differences in the OLS estimate of the treatment effect from 5.5 to 5.7 and the IV estimate of the treatment effect from 6.2 to 6.8. In summary, we find the that varying the patent status variable within reason matters little for our coefficients of interest.

If drugs with higher Medicare market shares were experiencing an increase in shortages prior to the policy change, then the coefficient estimate would be misinterpreted as evidence that the policy change led to an increase in shortages. Table 6 presents a falsification test by choosing a "pseudo"-regulation period and seeing whether our specification picks up the results. We use 2003 as the regulation year, rather than 2005, and drop all data starting in 2005. Thus, 2001 and 2002 are the fake pre-period and 2003 and 2004 are the post-period. The OLS coefficient from the MMS interacted with a post regulation indicator falls from 5.7 to .6 in this falsification test and loses statisitical significance. Likewise, the IV coefficient falls from 6.6 to 2.6 and loses statistical

[28] In the first two columns of Table 14 in the Appendix, we report the results using levels instead of logs. The results are qualitatively similar.

significance as well. These results suggest in the pre-period, the parallel trends assumption holds, a check that is often used in the literature to justify the parallel trends-assumption during the sample period.

To better understand how the effects of MMS change overtime, Table 7 presents the OLS and IV estimates of our specification using yearly treatment indicators interacted with the MMS. The OLS coefficient for 2007 is 5.215, which suggests a .58 day difference in shortages for drugs with .09 MMS versus those with .1 MMS, compared to the omitted year of 2001. The coefficients prior to 2004 are insignificant. In 2004 the magnitudes of both the OLS and the IV start growing and the coefficient estimates start becoming statistically different than zero. This corresponds to the switch from 95% AWP to 85% AWP in 2004 to $ASP + 6\%$ in 2005. Afterwards, the coefficients stabilize at higher levels, roughly 7 for the OLS and 9 for the IVs until the end of the sample. This highlights how consistent the coefficients are – results aren't due to just one year – and highlights some lag time for the MMA to matter for drug shortages.

Finally, since our theoretical model suggests that the MMA should impact off-patent drugs more than on-patent drugs with higher margins, we interact the patent indicator with pre and post regulation indicators and the MMS measure. Column (1) and (2) of Table 8 shows the OLS and IV estimates, respectively. The OLS coefficient estimate for off patent, post-regulation is 25 – suggesting that on average off-patent drugs in the post regulation period experience 25 days more of shortage than on patent drugs, prior to the regulation. The coefficient for off-patent, post-regulation interacted with the MMS of suggests that an off-patent drug with an MMS of .1 would have .83 more average days of shortage than a drug with an MMS of .09, relative to the difference between a comparable set of drugs, with the same MMS difference, that are on-patent and in the pre-regulation period. This is much larger than the same effect for drugs on patent, post-regulation (coefficient of 2.0) or off-patent but before ASP (coefficient of .06). Column (3) and (4) of Table 8 provide a falsification test where we show the result using 2 years after earliest approval as the definition of off patent. The magnitudes of the coefficients are smaller (7.45 to 1 for the OLS, 8.24 to .31 for IV) and no longer significantly significant. While previous results provided evidence for the role of MMA in shortages, this table corroborates our theory that off-patent drugs should be most affected by MMA, which we hypothesize is due to low reimbursement.

Table 2: OLS and IV Estimates of the Effect on MMS on Shortage Days

Dependent variable: Shortage Days in a Year

	(1)	(2)	(3)	(4)	(5)
Off Patent	-4.302	-4.423	-4.441	-8.390	-5.897
	(11.96)	(11.91)	(11.91)	(12.27)	(11.90)
Year $\geq$ 2005 $\times$ Log MMS	5.666***	6.554***	6.687***	7.047***	9.624***
	(1.641)	(2.023)	(2.014)	(2.207)	(2.811)
Constant	21.97**			23.55***	
	(8.509)			(8.479)	
Observations	2949	2949	2949	3429	2949
# Drugs	256	256	256	296	256
R^2	0.161	0.161	0.161	0.136	0.161
Drug Fixed Effect	Yes	Yes	Yes	Yes	Yes
Year Fixed Effect	Yes	Yes	Yes	Yes	Yes
IV Regression	No	Yes	Yes	No	Yes

Stars indicate statistical significance: *0.10, **0.05, ***0.01

Standard errors, in parentheses, are clustered at the drug level. Off patent is 15 years since Orange Book earliest approval. Columns (1) and (2) are the OLS and IV estimates using the IMS MMS as the treatment variable, respectively. Column (3) includes age in the instrument set. Column (4) and (5) are the OLS and IV estimates using the MarketScan MMS as the treatment variable. Each regression contains molecule fixed effects and indicator variables for each year from 2002 to 2012. Column (4) has more observations because the MarketScan data had associated HCPCS codes which improved our matching compared to name matching.

Table 3: First Stage - MarketScan MMS on IMS MMS

	(1)	(2)	(3)
Log MMS	1.279***	1.233***	0.583***
	(0.0469)	(0.0512)	(0.0214)
Mean Age		-0.0368	
		(0.0974)	
Mean Age Squared		0.000850	
		(0.00116)	
Constant	-0.831***	-1.089	-0.316**
	(0.181)	(2.061)	(0.126)
Observations	256	256	256
R^2	0.746	0.751	0.746
F-stat	744.7	253.3	744.7

Stars indicate statistical significance: *0.10, **0.05, ***0.01

Standard errors, in parentheses, are clustered at the drug level. First step in IVs. OLS with log of MarketScan MMS as the independent variable and log of IMS MMS as the dependent variable. Column (1) is the single instrument case. Column (2) adds age instruments. Column (3) uses log of MarketScan MMS as the dependent variable and log of IMS MMS as the independent variable.

Table 4: First Stage - Interaction of Predicted MMS with ASP Reimbursement

	(1)	(2)	(3)
Off Patent	-0.173	-0.204	0.166*
	(0.159)	(0.150)	(0.0844)
Predicted Log MMS	0.982***	0.984***	1.010***
	(0.0378)	(0.0365)	(0.0576)
Observations	2949	2949	2949
# Drugs	256	256	256
R^2	0.920	0.921	0.915
F-stat	217.4	220.4	171.0

Stars indicate statistical significance: *0.10, **0.05, ***0.01

Standard errors, in parentheses, are clustered at the drug level. This is the first-stage in 2SLS where the instrument is predicted MMS from Table 3 interacted with ASP Reimbursement. The first column in the main specification. The second is using age as an additional instruments. The third uses the MarketScan MMS instead of the IMS MMS. Each regressions also contains indicator variables for each year from 2002 to 2012, which are omitted from the table.

Table 5: Robustness Check: Different Patent Definitions

Dependent variable: Shortage Days in a Year

	(1)	(2)	(3)	(4)	(5)	(6)
Off Patent	58.28***	58.19***	-18.13	-17.98	-35.91***	-36.29***
	(16.95)	(16.83)	(11.38)	(11.30)	(8.618)	(8.653)
Year $\geq$ 2005 $\times$ Log MMS	5.536***	6.213***	5.600***	6.478***	5.789***	6.797***
	(1.615)	(1.966)	(1.658)	(2.047)	(1.640)	(2.033)
Constant	-9.252		30.15***		52.08***	
	(9.730)		(7.998)		(8.667)	
Observations	2949	2949	2949	2949	2949	2949
# Drugs	256	256	256	256	256	256
R^2	0.171	0.171	0.163	0.162	0.164	0.164
Drug Fixed Effect	Yes	Yes	Yes	Yes	Yes	Yes
Year Fixed Effect	Yes	Yes	Yes	Yes	Yes	Yes
IV Regression	No	Yes	No	Yes	No	Yes

Stars indicate statistical significance: *0.10, **0.05, ***0.01

Standard errors, in parentheses, are clustered at the drug level. This is table varies the years since earliest approval used as patent expiration. Columns (1) and (2) are the OLS and IV estimates with off-patent defined as 18 years since Orange Book earliest approval. Columns (3) and (4) are the OLS and IV estimates with off-patent defined as 12 years since Orange Book earliest approval. Columns (5) and (6) are the OLS and IV estimates with off-patent defined as 2 years since Orange Book earliest approval. Each regression contains molecule fixed effects and indicator variables for each year from 2002 to 2012.

Table 6: Falsification Test: Using 2003 as regulation year

Dependent variable: Shortage Days in a Year

	(1)	(2)
Off Patent	18.79	17.42
	(20.88)	(20.96)
Year $\geq$ 2003 $\times$ Log MMS	0.637	2.642
	(1.604)	(1.853)
Constant	11.80	
	(14.65)	
Observations	925	918
# Drugs	240	233
R^2	0.0517	0.0496
Drug Fixed Effect	Yes	Yes
Year Fixed Effect	Yes	Yes
IV Regression	No	Yes

Stars indicate statistical significance: *0.10, **0.05, ***0.01

Standard errors, in parentheses, are clustered at the drug level. This regression uses 2003, rather than 2005, as a false policy year. 2003 and 2004 are considered treatment years, data from 2005 and onwards are dropped. Off patent is 15 years since Orange Book earliest approval. Columns (1) and (2) are the OLS and IV estimates using the IMS MMS as the treatment variable, respectively. Each regression contains molecule fixed effects and indicator variables for each year from 2002 to 2012.

Table 7: OLS and IV Year By Year Coefficient Estimates

Dependent variable: Shortage Days in a Year		
	(1)	(2)
Off Patent	-3.681	-4.590
	(11.96)	(12.02)
Year=2002 × Log MMS	-0.473	0.0642
	(1.938)	(2.080)
Year=2003 × Log MMS	0.232	1.418
	(2.293)	(2.667)
Year=2004 × Log MMS	1.321	4.777**
	(2.071)	(2.314)
Year=2005 × Log MMS	4.050*	6.103**
	(2.136)	(2.584)
Year=2006 × Log MMS	3.478*	5.007*
	(2.057)	(2.601)
Year=2007 × Log MMS	5.215**	7.271***
	(2.037)	(2.786)
Year=2008 × Log MMS	6.474***	9.180***
	(2.236)	(2.671)
Year=2009 × Log MMS	6.097**	9.889***
	(2.385)	(2.725)
Year=2010 × Log MMS	7.073***	9.784***
	(2.483)	(2.588)
Year=2011 × Log MMS	8.105***	10.18***
	(2.905)	(3.147)
Year=2012 × Log MMS	7.201**	8.229**
	(3.067)	(3.258)
Constant	21.56**	
	(8.545)	
Observations	2949	2949
# Drugs	256	256
R^2	0.163	0.162
F-stat	9.778	9.843
Drug Fixed Effect	Yes	Yes
Year Fixed Effect	Yes	Yes
IV Regression	No	Yes

Stars indicate statistical significance: *0.10, **0.05, ***0.01

Standard errors, in parentheses, are clustered at the drug level. Columns (1) and (2) are the OLS and IV estimates, respectively. Each regression contains molecule fixed effects and indicator variables for each year from 2002 to 2012