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.

(JEL L11, L51, L65)

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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]

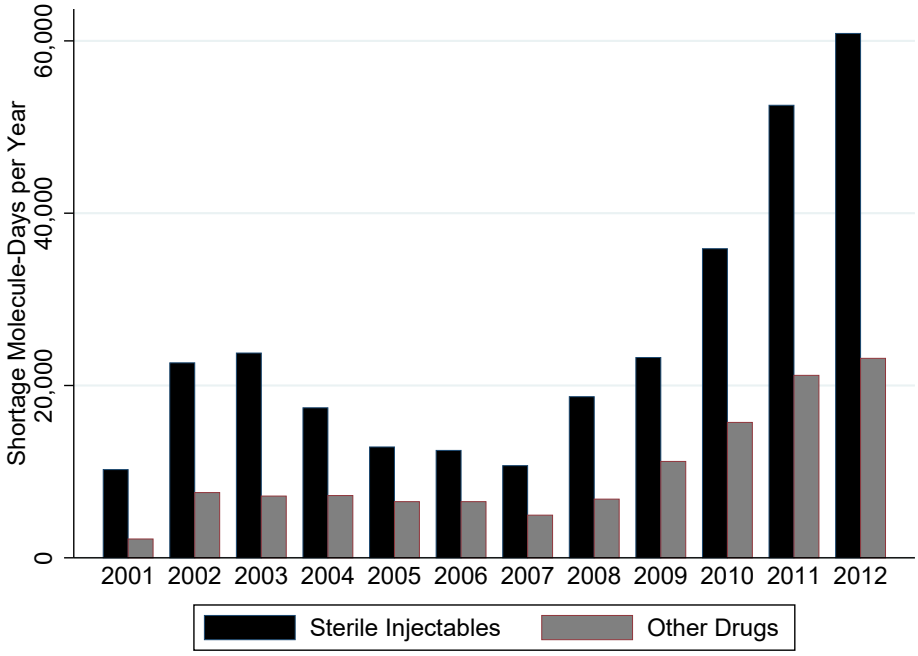

Figure 1: *Shortage days per year across all drugs. Source: University of Utah Drug Information Service*

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 health care providers that administer these drugs.[3] We be-

[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 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.

gin 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 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.[5] We then explore the mechanisms in our theoretical model. We show that drugs for which reimbursements fell more after the policy change had greater increases in shortages. The results hold whether measuring reimbursement from Medicare to health providers (which the policy directly affected, but which only indirectly affects profit) or a manufacturers' average revenue per dose (which the policy only indirectly affected, but which directly affects profit).

The median drop in reimbursement from Medicare to providers for generic sterile injectable drugs after the policy change was about 50%. We estimate that a 50% drop in reimbursement to providers would increase the number of expected shortage days by 16 per year from a mean of 60.

1 Background

The pharmaceutical industry is highly regulated. Approval by the US Food and Drug Administration (FDA) is required before manufacturers may market branded or generic prescription drugs. A manufacturer of a branded drug must demonstrate efficacy and safety compared to a placebo. Likewise, a manufacturer of a generic drug must demonstrate 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).

Sterile injectable drugs are typically administered in a clinical setting, such as a physician's

[4] See also Woodcock and Wosinska (2012).

[5] Our MMS measure is similar to the Medicare market share measure used by Duggan and Scott Morton (2010) who study the effect of introducing Medicare Part D.

office or in a hospital. According to our IMS Health data sample (which we detail later), injectable drug sales totaled $83 billion dollars and 3.7 billion units were dispensed in 2010. In the U.S. a typical generic sterile injectable drug is produced by three to four of the seven big generic injectable manufacturers.[6]

Sterility is critical for injectable drugs because they are administered intravenously, intramuscularly, or subcutaneously rather than passing through the gastrointestinal tract. Manufacturing lines must not 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 have been affected by the same supply shock, might not find it profitable to produce more units of the drug given capacity constraints, or might not be licensed to produce the drug.

Consider the following example of the supply chain for a sterile injectable drug (Figure 2). A patient who is over age 65 is eligible for Medicare and 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.[7] 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 (Medicare Part A), as well as physician visits and outpatient services (Medicare Part B). Under Part B, physicians are reimbursed when they administer a drug (often a sterile injectable).

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

[7] 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.

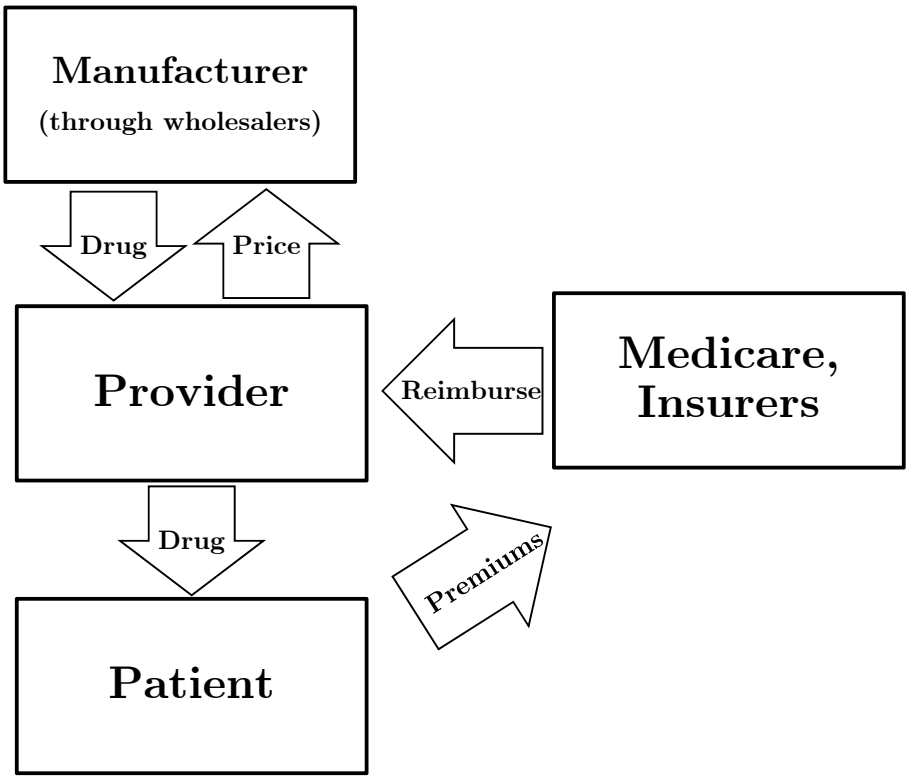

Figure 2: A provider purchases a drug from a manufacturer (through a wholesaler), then administers the drug to a patient. Medicare or a private insurer reimburses the provider for the drug.

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 Commission (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. The 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.[8] 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.[9]

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 – it is cost-based reimbursement – but it substantially reduced reimbursements.[10]

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

[9] For example, the US Department of Justice sued Abbott for violating the False Claims Act by reporting a high AWP for its products, including an intravenous antibiotic. For more information, see https://www.justice.gov/opa/pr/pharmaceutical-manufacturers-pay-4212-million-settle-false-claims-act-cases.

[10] The fact that ASP is based on two quarters previous introduces some rigidity into the price mechanism which likely does not 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.

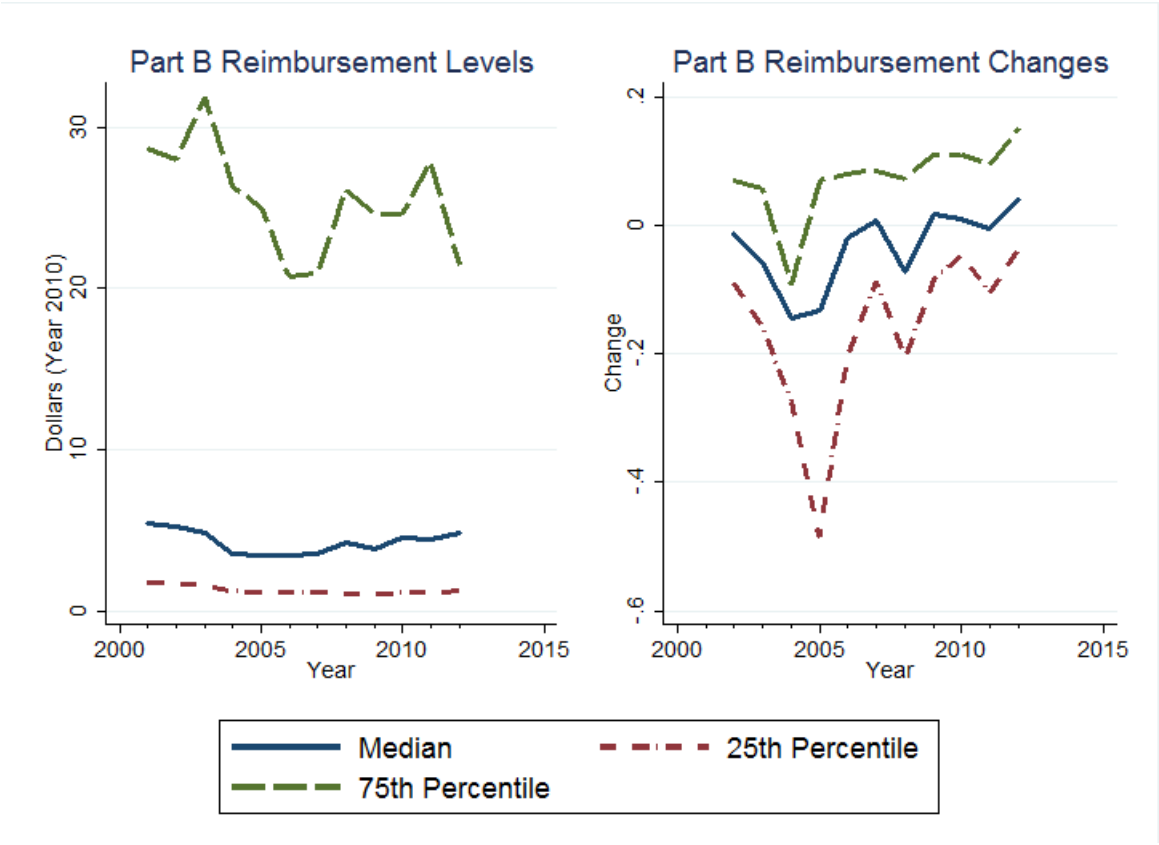

Figure 3: Medicare Part B reimbursement levels and changes for off-patent drugs. The left panel is the unweighted distribution of the reimbursement level, and the right panel is the unweighted distribution of reimbursement changes.

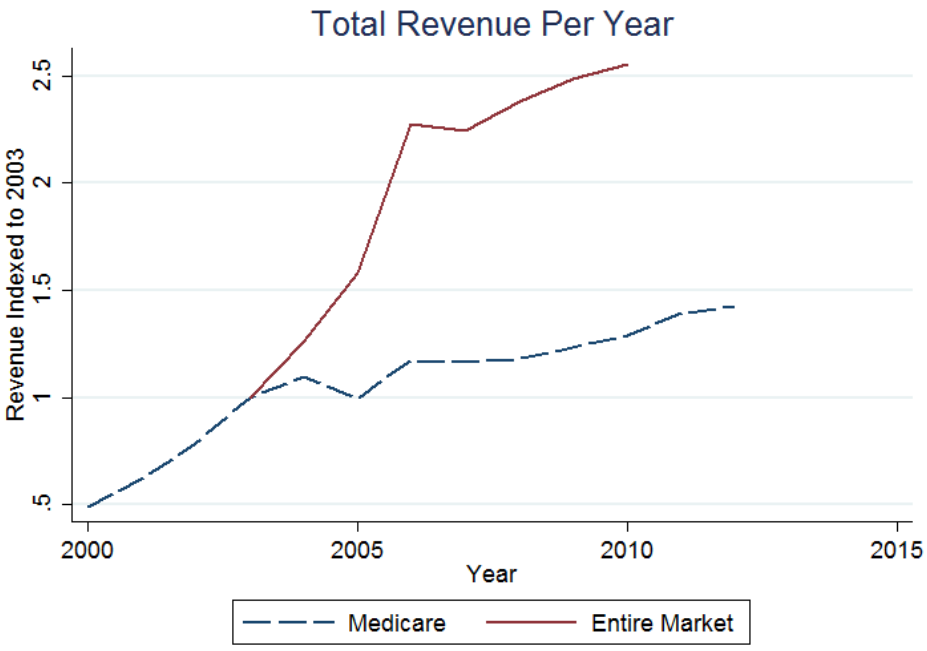

Figure 4: The top line is revenue for the drugs in our IMS data sample. The bottom (dashed) line is total reimbursement for Medicare Part B drugs indexed to 2003. This is the entire sample of HCPCS codes starting with J in the Part B summary files.

The MMA dramatically reduced reimbursement to providers for many generic drugs. Before the MMA, there was a large spread between the low generic price paid by providers and the high reimbursement provided by the government and other payers. After the MMA, reimbursement fell, putting financial stress on providers who sometimes changed treatment patterns, including changing drug regimens. For example, some providers changed from carboplatin and paclitaxel to docetaxel (Jacobson et al., 2010). The change also put downward pressure on generic prices. Hence, generic manufacturers might see profit fall due to changes in both quantity and price.

The reimbursement change directly affected Medicare fee-for-service. Private insurance and Medicare Advantage, which is administered by private insurers, were not directly affected.[11] 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 policy makers should know that private insurers often imitate Medicare.

The MMA not only affected Medicare Part B reimbursement, but also created Medicare Part D. Beginning in 2006, Medicare Part D provided prescription drug insurance to seniors and the disabled for drugs dispensed by pharmacists, drugs which are disproportionately oral solids (pills and tablets). The introduction of Medicare Part D might shift demand to oral solids, reducing demand for injectable or infused drugs. Reductions in demand for injectable or infused drugs would not directly cause shortages (just the opposite) but in the long run could reduce profit and the incentive to manufacture a drug.

A second change in reimbursement was the expansion of the Medicaid 340B program with more drugs purchased by covered entities. Drug purchases under the 340B Program account for

[11] Enrollment in Medicare Advantage was 13 percent of Medicare enrollees in 2005 and 27 percent in 2012.

about 2 percent of all U.S. drug purchases (U.S. Department of Health and Human Services, 2013, 311). The program requires that drug manufacturers offer discounts to outpatient facilities that can be classified as safety-net providers for low-income patients. Because these drugs are offered at a discount, the growth implies lower revenue for drug manufacturers.[12] Our estimates do not isolate the effect of reduced incentives because of 340B. However, both MMA and 340B reduced incentives because of government policies that affect reimbursement and prices.

1.2 Surplus for Providers and Manufacturers

Prior to the policy change, reimbursement to providers was typically much higher than the prices they paid, so 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 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.

The 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 reduced the prices manufacturers receive as well. We investigate the relationship between provider reimbursement and manufacturer price.

[12]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).

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.[13]

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 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 reimburses hospitals and physicians for drugs used for Medicare patients at p_{max} no matter what price the hospital or physician paid for the medicine.[14] 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

[13] 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.

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

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:

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

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

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

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 than necessary to serve the whole market, the manufacturers split the Medicare market according to what fraction of total capacity they own.[15] 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

[15]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.

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:

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

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

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

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 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.[16] 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

[16] 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.

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 a combination of active ingredients. For example, the nutritional product Multiple Vitamins for Infusion (MVI) 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 reimbursement data from the CMS Part B National summary files. Second, we use privately-insured outpatient hospital (analogous to Medicare Part B) reimbursement and quantity data from the MarketScan Commercial Claims and Encounters Database. Third, we use total US drug revenue and quantity data across all payers (Medicare, Medicaid, private insurance) and settings (physicians, hospitals, retail) from IMS Health. Fourth, we use shortage data by molecule and year from the University of Utah Drug Information Service. Fifth, we use 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.

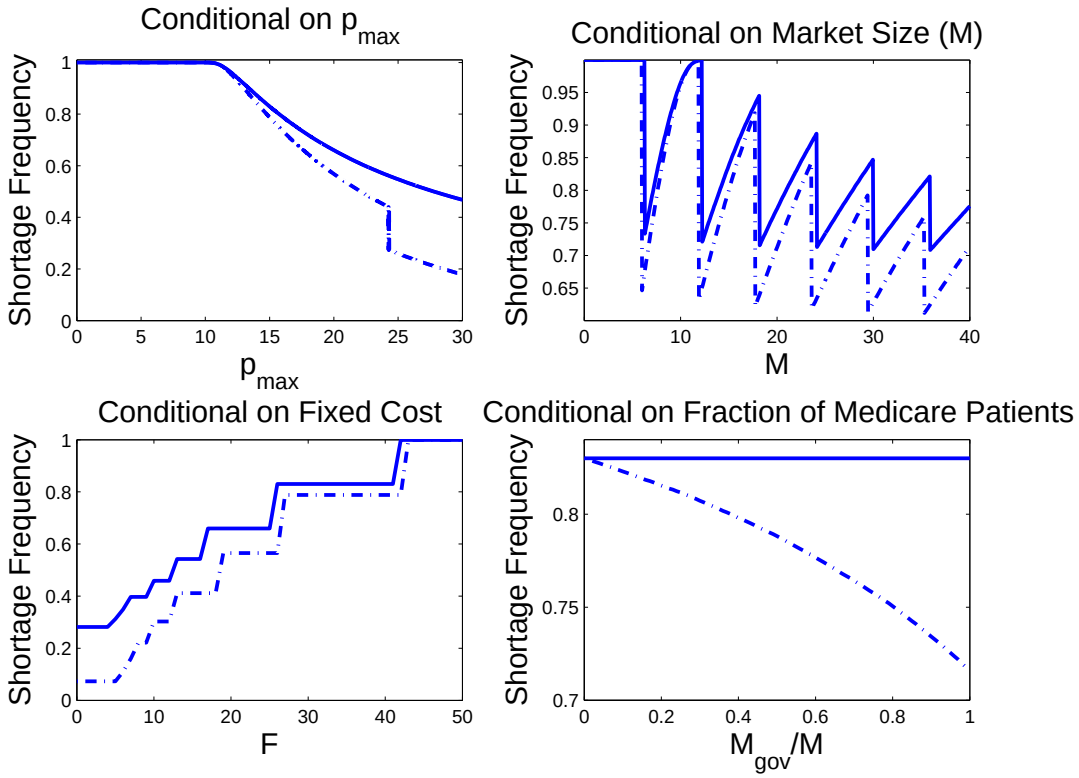

Figure 5: The model's predictions of shortage frequency as functions of model parameters. The solid lines are predictions for the cost-based ASP reimbursement regime. The dashed-dotted lines are predictions under the AWP reimbursement regime. Increasing p_{max} makes capacity investment more desirable and can induce entry. Increasing market size makes entry more desirable as there are more consumers for the medicine, but requires more capacity 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 reimbursement regime while it is unaffected in the ASP reimbursement regime.

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.

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 commercially-insured population in the U.S. We use the years 2001-2009 to estimate the total non-Medicare spending by year and HCPCS, adjusted for inflation to year 2010 dollars.

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 estimate sales to providers. These data contain all payers, including private, Medicare, Medicare Advantage, and Medicaid. Quantities are measured in standard units which can be thought of as doses, for injectable drugs, this is often an ampoule or vial. The IMS Health sales data do not include off-invoice discounts (for example, rebates paid by the manufacturer).

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 specific to a molecule and form (injectable or not) and for the 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.[17]

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[18] 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. We include these drugs but treat them all as single-source, on-patent drugs during our sample period, because Congress did not create a pathway for FDA to approve multi-source biologics (biosimilars) until 2010.

3.1 Medicare Market Share (MMS)

MMS is the fraction of a drug's reimbursement 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 reimbursement.[19] The two MMS measures vary according to the denominator: total reimbursement. In the first measure of MMS, the denominator is the sum of payments to manufacturers for each drug from the IMS database. In the second measure of MMS, the denominator is the sum of reimbursement for each drug in the MarketScan database plus the reimbursement in Medicare

[17] An alternative set of 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).

[18] 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.

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

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 reimbursement by drug as if the sample were nationally representative.[20] For example, suppose there are 10 million individuals in a given year in the MarketScan data. We scale the reimbursement 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, represent the population of drugs 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 reimbursement from Medicare to doctors. Nonetheless, it is a measure of the relative importance of Medicare 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.[21]

[20]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.

[21]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.

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,[22] in the period 2001 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,[23] we determine the relevant active ingredient(s) and route of administration by examining the HCPCS description and searching the FDA Orange Book.[24] This leaves 616 unique HCPCS J codes whose active ingredient(s) and route of administration have a match in the FDA Orange Book or are a biologic drug. We keep drugs whose route of administration is "injection," leaving 511 HCPCS J codes. Some drugs have multiple dosages with different HCPCS J codes. The 511 HCPCS codes correspond to 424 drugs.

Next, we join these data to the Medicare reimbursements from the Part B National Summary File by HCPCS code and year. We only keep HCPCS-year observations which were in the Part B National Summary File. This reduces the sample to 415 drugs. Next, we merge in the MarketScan MMS data by drug.[25] There are thirty additional active ingredients which never manifest in the MarketScan data and are dropped (leaving 385 drugs in our sample). Many of these drugs are introduced after 2009, which is the last year that we have MarketScan data.

We join these data to two FDA datasets by active ingredient(s) and year. The Orange Book is the primary FDA data set we use, but it does not include biologics so we supplement it with data from the drugs@FDA website. We keep all overlapping observations that either appear in the Orange Book or appear in the drugs@FDA website with a Biologics License Applications (BLA) number. There were nine drugs dropped because they neither appeared in the Orange Book nor on the drugs@FDA website with a BLA.

Next, we join this set of drugs to the IMS MIDAS data by year, active ingredient(s). The

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

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

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

[25] This is a mean across the sample years 2001-2009, so there is one observation for each drug.

matching is done by ingredient name, so it is imperfect. We were unable to match fifty drugs. Then, sixteen drugs were dropped because their MMS was greater than one or there was no spending in the IMS data, even if the drugs were matched. This leaves the sample of drugs which have a MarketScan MMS, IMS MMS and Medicare Reimbursement information at 310. We dropped two more drugs because they are only in the Medicare Reimbursement files for one year, which precludes their use in fixed-effect regressions.

We join this set of drugs to the shortage data by year, active ingredient(s), and route of administration. If an observation from the sample of drugs does not match to any shortage observation, we record that drug as not having shortages in the period of the sample. We do not drop any drugs while merging in the shortage data.

The final sample has 308 drugs. This corresponds to 3094 observations. Some drugs do not have 12 years in our data because they are not in the Part B summary files for 12 years. Of the 308 drugs in the sample, 102 are always on-patent, 111 are always off-patent, and the other 95 switch from on-patent to off during the sample period. The full list of drugs in the sample is in Appendix A.

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). 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 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 use logged Medicare market share because the observed distribution of MMS is skewed. Similarly, we use logged prices. 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 compute one MMS measure for each drug. In the appendix (Table 13) we show that the results are robust to using levels rather than logs of MMS, and using an MMS measure only using years prior to implementation.

4.1 Shortages Conditional on Medicare Market Share

First, we test the hypothesis that drugs most affected by the ASP reimbursement, that is, drugs with a large fraction of their revenues from Medicare Part B, experience larger increases in shortages. We use a difference-in-difference model where the first difference is the Medicare (Part B) Market Share (MMS_i) of drug i and the second difference is before and after the policy change ($Post_t$). 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. The model includes α_i and δ_t which 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 "post" (the indicator variable for years 2005 and

[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.

later), 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 post variable. This interacted value serves as the instrumental variable for the interaction of the post variable and the IMS MMS measure in a standard two stage least squares procedure.

We include several 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.

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:

[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.

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

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, we 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:

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

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 concern 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 Medicare is a subset of the market, the MMA might not be not solely responsible for overall price changes. 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. Figure 6 demonstrates the identifying variation. There were considerable price declines for the highest MMS drugs (left panel of Figure 6) with the highest prices (dashed line). These drugs were most likely to have inflated AWP before the reimbursement change, and would have had the biggest sales impact due to their high Medicare shares.

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 IMS price, a measure of manufacturer's prices, on the Medicare reimbursement per service, a measure of reimbursement to providers. Also, to show that this effect is strongest for drugs where Medicare plays a larger role, we interact the MMS with the Medicare

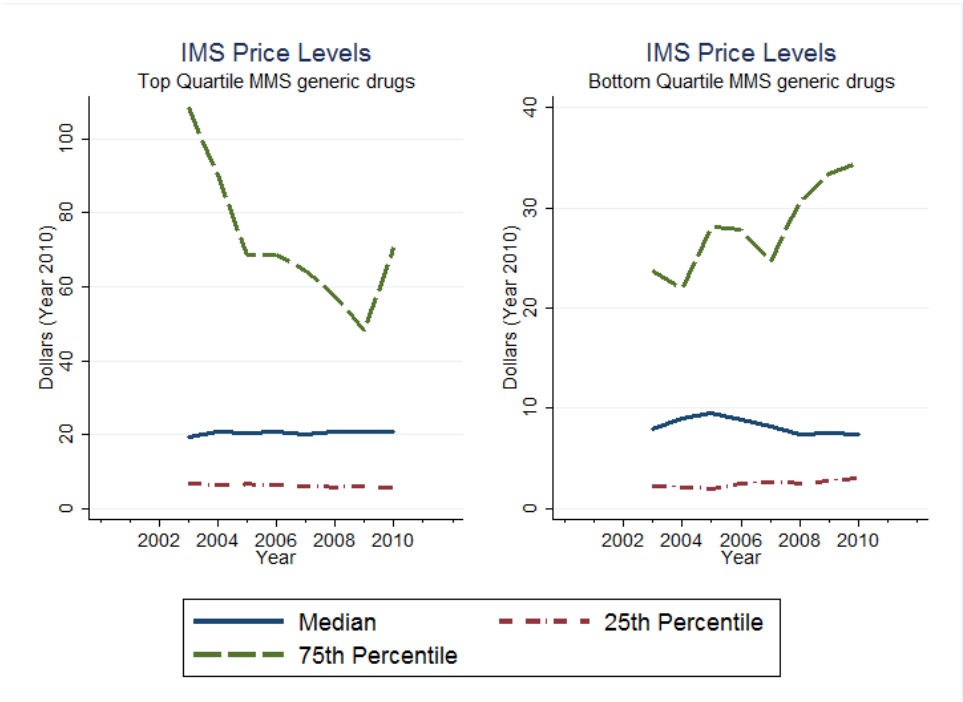

Figure 6: On the left are price levels for drugs in the top quartile of MMS, meaning used by seniors. The prices are falling for the highest price drugs targeted at seniors. On the right are price levels for the bottom quartile of MMS, meaning used by younger patients. All percentiles are calculated without weights across drugs.

reimbursements. Formally, this is modelled as:

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

5 Results

The top panel of Table 1 gives summary statistics for the main sample. There are 308 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 59 days (unconditional on being in shortage), but was 82 days and 14 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. Using the IMS data, the average MMS is 0.10 and using the MarketScan data the average MMS is 0.15. The MarketScan MMS measure is larger because it does not include in the denominator spending by payers like Medicare Advantage, Medicaid or Veteran's Affairs or payments from settings like inpatient hospitals. In the MarketScan data, the mean patient age is 45.

There are fewer observations in the Manufacturer Price and Number of Manufacturers rows. Manufacturer Price has fewer observations, because our sample of IMS data is from 2003 to 2010, so earlier and later years are dropped. The Number of Manufacturers row has fewer observations because some drugs were not in the Orange Book. Many of the products missing from the Orange Book are biologics which we assume are on patent (or at least, have no generic competition). Hence, while many of the observations are missing from the Orange Book, they are not missing from our analysis.

Figure 3 shows the distribution of reimbursement levels (left panel) and changes (right panel) for off-patent drugs in Medicare. In 2005, there is a large fall in reimbursement which is concurrent with the implementation of ASP under the MMA. Figure 7 in the appendix shows the distribution for all drugs (on and off patent), which has similar patterns, though less pronounced.

Figure 6 shows that IMS prices decline most for generic drugs with high prices and high MMS.

The left panel shows prices for drugs in the bottom quartile of share of their sales from Medicare, while the right shows the drugs in the top quartile. We see large, slow price declines in drugs that have a high share of Medicare sales versus those which do not. 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 is not 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, prices fall over time in all markets as other payers switch to ASP. This may help explain the lag in shortages after the law change.

Table 1: Summary Statistics

	source	count	mean	sd	min	max
Shortage Days	Univ. Utah	3094	59.28	120.23	0.00	365.00
Number of Manufacturers	Orange Book	2679	3.04	2.94	0.00	25.00
MMS	IMS	3094	0.10	0.17	0.00	1.00
MMS	MarketScan	3094	0.15	0.17	0.00	0.93
Medicare Reimbursement ($)	Part B	3094	81.03	261.96	0.00	3645.59
Mean Age (years)	MarketScan	3094	45.34	7.42	12.83	57.92
Off Patent	Orange Book	3094	0.66	0.47	0.00	1.00
Manufacturer Price ($)	IMS	2030	286.90	672.92	0.01	12533.00
Observations		3094				

		Off Patent			On Patent		
	source	count	mean	sd	count	mean	sd
Shortage Days	Univ. Utah	2050	82.40	135.77	1044	13.87	59.48
Number of Manufacturers	Orange Book	2050	3.68	3.09	629	0.95	0.22
MMS	IMS	2050	0.09	0.16	1044	0.14	0.19
MMS	MarketScan	2050	0.13	0.15	1044	0.19	0.20
Medicare Reimbursement ($)	Part B	2050	32.40	118.54	1044	176.52	402.64
Mean Age (years)	MarketScan	2050	44.42	6.83	1044	47.14	8.17
Off Patent	Orange Book	2050	1.00	0.00	1044	0.00	0.00
Manufacturer Price ($)	IMS	1315	93.47	383.64	715	642.66	905.71
Observations		2050			1044		

Summary statistics from 2001 to 2012 for the 308 drugs in the sample. MMS is Medicare Market Share.

5.1 Results for Shortages Conditional on Medicare Market Share

Table 2 presents the difference-in-differences relationship between shortages and Medicare market share. Columns (1) and (2) OLS and IV give the estimates without age in the instrument set. Using year indicators, we have differenced out the time-trend in the results. The OLS estimate of β is 6.73, while the IV estimate is 7.83. 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 .10 leads to a 0.71 and 0.82-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. Columns (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 implied magnitudes. The IV coefficient of 12.88 implies a change from .14 to .15 in MMS, leads to a 0.89-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. In the main specification we assume the patent expires 15 years after the first approval. Here, 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 8 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

[28] In the first two columns of Table 13 in the Appendix, we report the results using levels instead of logs. The results are qualitatively similar.

variable leads to differences in the OLS estimate of the treatment effect from 6.29 to 6.77 and the IV estimate of the treatment effect from 7.11 to 7.88. 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 6.73 to -0.61 in this falsification test and loses statistical significance. Likewise, the IV coefficient falls from 7.83 to 1.39 and loses statistical 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 over time, 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 6.63, which suggests a .70-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 2005 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 10 for the IVs until the end of the sample. This highlights that the results are not due to just one year, as well as some lag time for the MMA to matter for drug shortages.

Finally, because 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 positive at 15.19 – suggesting that on average off-patent drugs in the post regulation period experience

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	-5.200	-5.449	-5.454	-6.763	-7.576
	(13.54)	(13.51)	(13.52)	(13.57)	(13.46)
Year $\geq$ 2005 $\times$ Log MMS	6.732***	7.828***	7.852***	10.20***	12.88***
	(2.192)	(2.925)	(2.932)	(3.648)	(4.021)
Constant	17.70*			18.62**	
	(9.286)			(9.287)	
Observations	3094	3094	3094	3094	3094
# Drugs	308	308	308	308	308
R^2	0.172	0.172	0.172	0.172	0.171
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 earliest Orange Book 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.

more shortages than on patent drugs, prior to the regulation, however this difference is statistically insignificant. The coefficient for off-patent, post-regulation interacted with the MMS suggests that an off-patent drug with a MMS of .1 would have .87 more average days of shortage than a drug with a 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 2.29) or off-patent but before ASP (coefficient of -0.93). Columns (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 1.09 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 3: First Stage - MarketScan MMS on IMS MMS

	(1)	(2)	(3)
Log MMS	1.223***	1.215***	0.561***
	(0.0473)	(0.0518)	(0.0217)
Mean Age		-0.198**	
		(0.0896)	
Mean Age Squared		0.00244**	
		(0.00108)	
Constant	-0.855***	2.946	-0.468***
	(0.175)	(1.873)	(0.120)
Observations	308	308	308
R^2	0.686	0.691	0.686
F-stat	668.0	226.6	668.0

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 - Predicted MMS $\times$ Year $\geq$ 2005

	(1)	(2)	(3)
Off Patent	-0.168	-0.180	0.184**
	(0.167)	(0.160)	(0.0791)
Predicted Log MMS	1.065***	1.063***	0.932***
	(0.0504)	(0.0507)	(0.0578)
Observations	3094	3094	3094
# Drugs	308	308	308
R^2	0.905	0.907	0.911
F-stat	177.0	176.0	166.4

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 instrument. The third uses the MarketScan MMS instead of the IMS MMS. Each regression 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	69.84***	69.55***	-10.51	-10.78	-19.92*	-19.83*
	(18.44)	(18.35)	(12.82)	(12.80)	(11.10)	(11.15)
Year $\geq$ 2005 $\times$ Log MMS	6.290***	7.108**	6.765***	7.877***	6.671***	7.703***
	(2.147)	(2.849)	(2.197)	(2.938)	(2.202)	(2.948)
Constant	-16.97*		20.48**		27.68***	
	(9.862)		(8.274)		(8.715)	
Observations	3094	3094	3094	3094	3094	3094
# Drugs	308	308	308	308	308	308
R^2	0.184	0.184	0.172	0.172	0.173	0.173
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 earliest Orange Book approval. Columns (3) and (4) are the OLS and IV estimates with off-patent defined as 12 years since earliest Orange Book approval. Columns (5) and (6) are the OLS and IV estimates with off-patent defined as 8 years since earliest Orange Book approval.[29] 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	29.83	27.47
	(26.14)	(26.52)
Year $\geq$ 2003 $\times$ Log MMS	-0.608	1.390
	(2.440)	(2.697)
Constant	3.340	
	(18.54)	
Observations	896	879
# Drugs	246	229
R^2	0.0633	0.0617
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 earliest Orange Book 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 2004.

Table 7: OLS and IV Year By Year Coefficient Estimates
Dependent variable: Shortage Days in a Year

	(1)	(2)
Off Patent	-5.635	-7.220
	(13.64)	(13.72)
Year=2002 × Log MMS	-2.036	-1.142
	(2.058)	(2.502)
Year=2003 × Log MMS	-1.789	-0.452
	(3.130)	(3.705)
Year=2004 × Log MMS	0.597	5.381
	(2.915)	(3.343)
Year=2005 × Log MMS	5.006*	8.252**
	(2.981)	(3.775)
Year=2006 × Log MMS	4.845*	7.353*
	(2.892)	(3.913)
Year=2007 × Log MMS	6.633**	10.09**
	(2.778)	(4.025)
Year=2008 × Log MMS	7.967***	12.07***
	(2.993)	(3.844)
Year=2009 × Log MMS	7.856**	13.39***
	(3.384)	(3.888)
Year=2010 × Log MMS	5.886*	10.04***
	(3.350)	(3.632)
Year=2011 × Log MMS	6.457	8.620*
	(3.940)	(4.650)
Year=2012 × Log MMS	2.908	3.181
	(3.976)	(4.755)
Constant	17.89*	
	(9.478)	
Observations	3094	3094
# Drugs	308	308
R^2	0.174	0.172
F-stat	10.88	11.10
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

Table 8: Interacting Patent Status and Treatment Status
Dependent variable: Shortage Days in a Year

	(1)	(2)	(3)	(4)
Off Patent × Year ≥ 2005	15.27	15.19	-36.50*	-39.25**
	(22.77)	(23.63)	(18.70)	(19.20)
Off Patent × Year<2005	-31.25	-36.99	-77.07***	-83.92***
	(26.19)	(29.49)	(18.83)	(22.52)
On Patent × Year ≥ 2005 × Log MMS	1.250	1.872	2.550	3.395
	(2.313)	(2.289)	(3.651)	(3.584)
Off Patent × Year ≥ 2005 × Log MMS	4.758	5.366	-2.393	-2.222
	(4.262)	(4.317)	(2.941)	(2.885)
Off Patent × Year<2005 × Log MMS	-5.231	-6.493	-12.09***	-13.68***
	(5.214)	(6.009)	(3.995)	(4.778)
Constant	20.03*		30.40***	
	(10.75)		(9.960)	
Observations	3094	3094	3094	3094
# Drugs	308	308	308	308
R^2	0.175	0.174	0.177	0.177
Drug Fixed Effect	Yes	Yes	Yes	Yes
Year Fixed Effect	Yes	Yes	Yes	Yes
IV Regression	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 table interacts the off-patent variable with the post MMA indicator and MMS. Columns (1) and (2) are the OLS and IV estimates with off-patent defined as 15 years since earliest Orange Book approval. As a falsification test, columns (3) and (4) are the OLS and IV estimates with off-patent defined as just 8 years since earliest Orange Book approval. Each regression contains molecule fixed effects and indicator variables for each year from 2002 to 2012.

Table 9: OLS and lagged OLS Estimates of Medicare Reimbursement Effect on Shortages

	(1)	(2)	(3)	(4)	(5)	(6)
Log Reimbursement	-26.88***	-30.29***	-32.19***	-40.27***	-8.506	-3.724
	(4.111)	(5.176)	(5.752)	(6.942)	(8.312)	(8.236)
Off Patent	-13.88	-17.04				
	(12.32)	(14.06)				
Constant	87.56***	225.6***	90.07***	266.9***	39.27	54.24**
	(12.74)	(16.61)	(12.21)	(13.71)	(28.71)	(27.31)
Observations	3093	2785	1295	1184	793	691
# Drugs	308	308	111	111	102	102
R^2	0.194	0.197	0.289	0.300	0.0474	0.0463
Lagged Reimbursement	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. Regresses Medicare reimbursement amounts on shortage frequency. Columns (1) and (2) are the OLS and 1-year lagged OLS estimates for all drugs. Off-patent defined as 15 years since earliest Orange Book approval. Columns (3) and (4) are the OLS and 1-year lagged estimates for drugs off-patent throughout the sample period. Columns (5) and (6) are the OLS and 1-year lagged estimates for drugs on-patent throughout the sample period. All regressions include year and ingredient fixed effects.

5.2 Results for Shortages Conditional on Reimbursements to Health Providers

Table 9 shows the results for shortages conditional on reimbursements to providers. Columns (1) and (2) show the log and lagged-log reimbursement coefficients. The coefficient on lagged reimbursement suggests that a 1 percent (roughly 81 cents per unit) decrease in reimbursement leads to .30 more shortage days. Columns (3) and (4) show the same results keeping only drugs which were off-patent throughout the sample while columns (5) and (6) show the on patent results. Consistent with our theory, off-patent drugs were most affected by prices. The statistically significant coefficient on a one-year lag of log price for an off-patent drug of -40.27 suggests that a 1 percent decrease in price (roughly 32 cents per unit) leads to .40 more shortage days. The on-patent drugs' results were negative and not statistically significantly different from zero, which is consistent with our theory that these drugs had higher margins. The change in estimates moving from current price to the 1 year lagged price (-26.88 to -30.29) are consistent with correcting the downward bias caused by the reverse causality problem described above.

5.3 Results for Shortages Conditional on Manufacturer's Prices

Table 10 shows the results for shortages conditional on manufacturer's prices. Columns (1) and (2) show the log and lagged-log price coefficients. The coefficient on lagged price suggests that a 1 percent (roughly 2.87 dollars per unit) decrease in price leads to .36 more shortage days. Columns (3) and (4) show the same results keeping only drugs which were off-patent throughout the sample while columns (5) and (6) show the on patent results. Again, off-patent drugs were most affected by prices. The statistically significant coefficient on 1 year lag of log price of -29.91 suggests that a 1 percent decrease in price (roughly 93 cents per unit) leads to .30 more shortage days. The on-patent drugs' results, as in the case with reimbursements to health providers, were not statistically significant. In summary it appears that lower prices to manufacturers are correlated with more shortages.

Table 10: OLS and lagged OLS Estimates of Manufacturer Price Effect on Shortages

	(1)	(2)	(3)	(4)	(5)	(6)
Log IMS Price	-20.04**	-35.84***	2.606	-29.91**	-1.303	-6.324
	(8.853)	(7.790)	(17.24)	(14.72)	(10.99)	(14.45)
Off Patent	-3.639	-39.85**				
	(14.63)	(15.48)				
Constant	158.1***	183.4***	73.37*	110.1***	36.56	57.17
	(34.60)	(27.90)	(38.42)	(32.01)	(69.15)	(82.36)
Observations	1948	1927	792	790	531	523
# Drugs	293	291	104	104	99	99
R^2	0.0677	0.189	0.101	0.267	0.0248	0.0231
Lagged Price	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. Regresses manufacturer prices (from IMS) on shortage frequency. Columns (1) and (2) are the OLS and 1-year lagged OLS estimates for all drugs. Off-patent defined as 15 years since earliest Orange Book approval. Columns (3) and (4) are the OLS and 1-year lagged estimates for drugs off-patent throughout the sample period. Columns (5) and (6) are the OLS and 1-year lagged estimates for drugs on-patent throughout the sample period. All regressions include year and ingredient fixed effects.

5.4 Results for Correlation in Payments to Providers and Manufacturers

Table 11 reports the correlation in payments. On average, a ten percent decline in Medicare reimbursement would reduce the manufacturer's price by 3.4 percent. Drugs which have higher

Table 11: Effect of Medicare Reimbursement on Price to Manufacturers

	(1)	(2)	(3)	(4)	(5)	(6)
Log Medicare Reimbursement	0.352***	0.339***	0.237***	0.206***	0.0582	0.0619
	(0.0524)	(0.0593)	(0.0508)	(0.0550)	(0.0371)	(0.0395)
Log Medicare Reimbursement × MMS		0.129		0.195		-0.125
		(0.187)		(0.182)		(0.178)
Constant	2.827***	2.809***	1.834***	1.828***	5.461***	5.518***
	(0.129)	(0.124)	(0.0824)	(0.0797)	(0.131)	(0.142)
Observations	2029	2029	848	848	533	533
# Drugs	304	304	111	111	100	100
R^2	0.284	0.285	0.164	0.172	0.0600	0.0615

Stars indicate statistical significance: *0.10, **0.05, ***0.01
Standard errors, in parentheses, are clustered at the drug level. This table regresses Medicare prices on IMS prices. Columns (1), (3) and (5) regress log Medicare price on IMS price, with year and drug fixed effects. Columns (2), (4) and (6) adds an interaction between Medicare market share with the Medicare price. Columns (1) and (2) are all drugs. Columns (3) and (4) are drugs which are off patent throughout the sample. Columns (5) and (6) are drugs which are on patent throughout the sample.

Medicare market share should be more affected by Medicare price changes. To account for this, we interact the share of revenue coming from Medicare. The interaction term, while statistically insignificant, is important in magnitude. Added to β_1, the coefficient implies that a 10 percent decline in Medicare reimbursement could reduce the price a manufacturer gets by close to 4.6 percent near the maximum on MMS. This is suggestive of the magnitude of pass-through in reimbursement reductions from the law to manufacturers.

6 Discussion

We analyzed the effect of the 2005 reimbursement change on drug shortages using several approaches. Our main approach was a difference-in-difference (pre/post and Medicare market share) with drug and year fixed effects. We found that the reimbursement change led to about 2 additional weeks (13 days) of shortages for generic injectables (Column 5 of Table 2). We also used a triple difference without fixed effects and again found that shortages of generic injectables increased by about 2 weeks (13 days) (Column 5 of Table 16). Finally, we used reimbursement on the right side of the regression equation to examine directly how reimbursement affected shortages. We found that a 50% drop in reimbursement (Office of Inspector General, 2005) led to about 2 additional weeks (16 days) of shortages for generic injectables (Table 9).

We provide evidence that higher reimbursement could reduce drug shortages. A 10% increase in Medicare reimbursement for an off-patent drug is associated with 4 fewer days of shortage (Table 9). A 10% increase on all off-patent drugs is about $3.24 per service (Table 1). With roughly 50 million services per year (699 million services across 12 years), and at $3.24 per service, that equals $162 million dollars to avert 4 days of shortages for the average injectable or infused drug. However, if the payment increases target lower-priced drugs, as would be sensible according to our model, then a reduction in shortages could be much more cost effective.[30] A payment increase of 10% for off-patent drugs under the 90th percentile of reimbursement levels would amount to $0.71 per service. For off-patent drugs below the 50th percentile, the increase would be $0.12 per service. Focusing on these least cost drugs, for example by targeting drugs in the lower half of the reimbursement level distribution, would allow for a reduction in total shortages of 12.5 days at a cost of about $50 million dollars.[31]

Other factors may also be associated with drug shortages. First, declining drug prices resulted not only from Medicare changes, but also from the expansion of 340B pricing (as discussed in section 1.1). However, the scale of the 340B program is much smaller than the scale of Medicare with the 340B program accounting for only about 2 percent of U.S. drug sales (U.S. Department of Health and Human Services, 2013, 311). Second, industry consolidation could cause shortages. However, consolidation among manufacturers has ambiguous effects. Consolidation could make shortages less likely as consolidation increases market power and margins. Alternatively, depending on the covariance of shocks to manufacturing lines of different firms, consolidation could lead to increased shortages. Third, shortages could be caused by grey-market distributors and stockpiling by hospitals. However, these practices are relatively rare and are symptoms of shortages, rather than causes. Finally, increased FDA regulatory scrutiny appears to be associated with drug shortages (Stomberg, 2015). However, some of the increased scrutiny could be a reaction to less investment in reliability by the manufacturers. The aforementioned factors are complementary hypotheses but are not valid competing hypothesis. For example, for FDA regulatory scrutiny to be a competing hypothesis, increased FDA scrutiny would have to take place after the policy change

[30] In columns (3) and (4) in Table 13 in the Appendix, we show that the main regression results hold within the sample of lower price generic drugs as defined by prices below the median.

[31] The total cost to society depends on how private payment reacts as well. If private payment follows Medicare reimbursement, then it would be more expensive. In fact, not all private insurers changed and even those that changed did not move all the way down to ASP plus 6%, so the cost would be less than $750 million.

and fall disproportionately on generic drugs which served more Medicare patients.

The policy change was implemented in 2005, but shortages did not become large until 2009. However, the empirical analysis shows an increase in shortages for drugs with higher MMS starting in 2006. Furthermore, as described in section 1.1, private insurers are known to mimic Medicare with a lag. Finally, some manufacturers probably continued to produce these low-margin drugs until other opportunities arose, such as following a large wave of patent expirations in 2007.

The generic sterile injectable market shares several features with electricity generation. First, timing is critical. In the generic market, delays can be costly to patient health, and in electricity, supply and demand must be in equilibrium at each instant to avoid power system failures. Second, storage is costly. Sterile injectables are sensitive to light and temperature. Likewise, storing electricity by battery or with hydro-storage is currently considered prohibitively costly in most cases. Third, there is little product differentiation, so price competition can be fierce. The solution in electricity generation has been a mixture of rapid price adjustment and government regulation (Cramton and Stoft, 2005).

7 Conclusion

Shortages of drugs, especially generic sterile injectable drugs, increased dramatically beginning in the mid-2000s. The increase in shortages followed a changed in drug reimbursement. We show that a reduction in reimbursement to health providers was passed to manufacturers and played a role in the large increase in shortages of generic sterile injectable drugs. Drugs that were most affected by the reimbursement change were drugs used to treat diseases with high Medicare share. While Medicare reimbursement does not directly explain the full increase in shortages, the evidence is consistent with a theoretical model in which declining Medicare reimbursement decreases the returns to investing in capacity and leading to an increased level of shortages.

To reduce shortages, Medicare could increase reimbursement. Indeed, both the theoretical model and the empirical results suggest that firms with market power (and thus higher prices) tend to invest more in capacity and have fewer shortages. However, increasing prices through higher reimbursement and/or market power is costly. The optimal number of shortages is not necessarily zero if it requires extremely high prices.

Another approach to reducing shortages would be to write contracts with "failure to supply" clauses. If contracts impose harsh penalties on manufacturers for failure to supply, then shortages should fall and average prices should rise. However, contracts might be difficult to enforce due to information asymmetries. Furthermore, contracts usually void the penalty in the case of nationwide shortages (U.S. Department of Health and Human Services, 2011). Another concern is that contracts might encourage the buyer to create a shortage by hoarding, thus receiving a penalty payment from the supplier. Alternatively, competing suppliers might hoard to create a shortage and then supply the product when prices rise. Given that the shortage problem is relatively recent, perhaps buyers will learn to write new contracts that reduce the shortage problem.

Finally, there might be a role for regulation. For example, the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 requires that manufacturers notify FDA of potential discontinuances.

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A Appendix

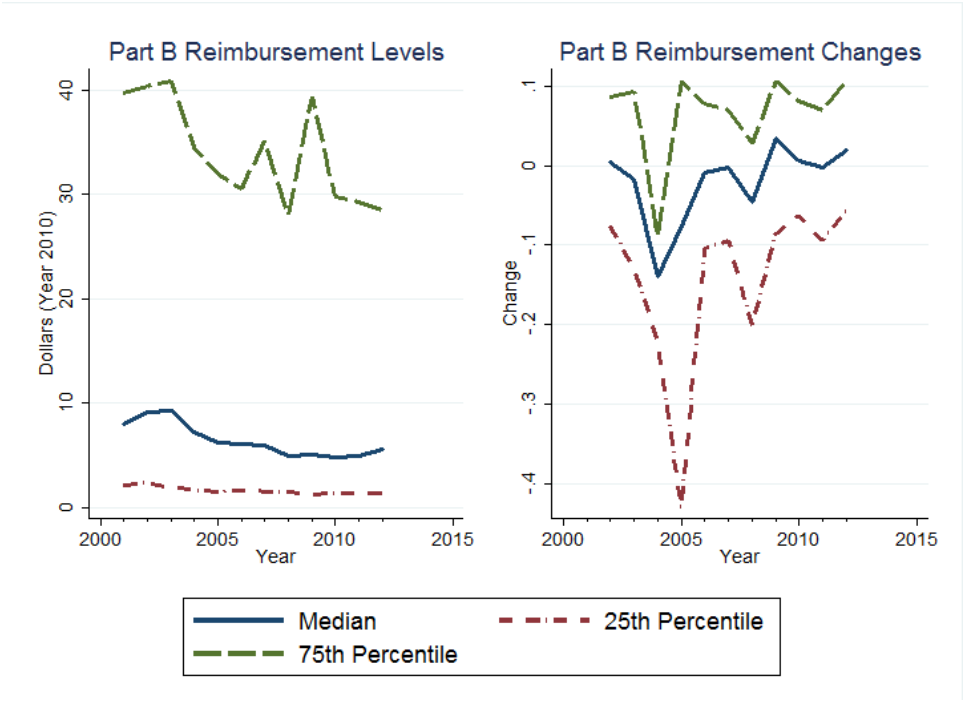

Figure 7: Medicare Part B reimbursement levels and changes for the full sample of drugs (on and off patent). The left panel is the unweighted distribution of the reimbursement level, and the right panel is the unweighted distribution of reimbursement changes.

Table 12: List of Drugs in the Sample

Abarelix
Abatacept
Abciximab
Acetazolamide sodium
Acetylcysteine
Acyclovir sodium
Adalimumab
Adenosine
Agalsidase
Alatrofloxacin mesylate
Aldesleukin
Alefacept
Alemtuzumab
Alglucosidase alfa
Alprostadil
Alteplase
Amifostine
Amikacin sulfate
Aminophylline
Amiodarone hydrochloride
Amitriptyline hydrochloride
Amphotericin b
Ampicillin sodium
Anadulafungin
Apomorphine hydrochloride
Aripiprazole
Arsenic trioxide
Asparaginase
Atropine sulfate
Azacitidine
Azithromycin
Basiliximab
Bcg
Bendamustine hydrochloride
Benztropine mesylate
Betamethasone sodium phosphate
Bevacizumab
Bivalirudin
Bleomycin sulfate
Bortezomib
Buprenorphine hydrochloride
Busulfan
Butorphanol tartrate
Caffeine citrate
Calcitriol
Carboplatin
Carmustine
Caspofungin acetate
Cefazolin sodium
Cefepime hydrochloride
Cefotaxime sodium
Cefoxitin sodium
Ceftazidime
Ceftizoxime sodium
Ceftriaxone sodium
Cefuroxime sodium
Cetuximab
Chloramphenicol sodium succinate
Chloroprocaine hydrochloride
Chlorothiazide sodium
Chlorpromazine hydrochloride
Cidofovir
Cilastatin sodium; imipenem
Ciprofloxacin
Cisplatin
Cladribine
Clofarabine
Clonidine hydrochloride
Colistimethate sodium
Corticorelin ovine triflutate
Corticotropin
Cosyntropin
Cyclophosphamide
Cytarabine
Cytomegalovirus
Dacarbazine
Daclizumab
Dactinomycin
Dalteparin sodium
Daptomycin
Darbepoetin
Daunorubicin hydrochloride
Decitabine
Deferoxamine mesylate
Denileukin
Desmopressin acetate
Dexamethasone acetate
Dexamethasone sodium phosphate
Dexrazoxane hydrochloride
Diazepam
Diazoxide
Dicyclomine hydrochloride
Digoxin
Digoxin immune fab
Dihydroergotamine mesylate
Dimenhydrinate
Diphenhydramine hydrochloride
Dipyridamole
Dobutamine hydrochloride
Docetaxel
Dolasetron mesylate
Dopamine hydrochloride
Doripenem
Doxercalciferol
Doxorubicin hydrochloride
Droperidol
Dyphylline
Eculizumab
Enoxaparin sodium
Epinephrine
Epirubicin hydrochloride
Epoetin
Epoprostenol sodium
Eptifibatide
Ertapenem sodium
Erythromycin lactobionate
Estradiol cypionate
Estradiol valerate
Estrogen conjugated
Etanercept
Ethanolamine oleate
Etoposide
Euflexxa
Fentanyl citrate
Filgrastim
Floxuridine
Fluconazole
Fludarabine phosphate
Fluorouracil
Fluphenazine decanoate
Fomepizole
Fomivirsen sodium
Fondaparinux sodium
Fosaprepitant dimeglumine
Foscarnet sodium
Fulvestrant
Furosemide
Gallium nitrate
Galsulfase
Ganciclovir sodium
Gatifloxacin
Gemcitabine hydrochloride
Gemtuzumab ozogamicin
Gentamicin sulfate
Glatiramer acetate
Glucagon hydrochloride
Gonadorelin hydrochloride
Gonadotropin, chorionic
Granisetron hydrochloride
Haloperidol decanoate
Haloperidol lactate
Heparin sodium
Hyaluronidase
Hydralazine hydrochloride
Hydrocortisone acetate
Hydrocortisone sodium phosphate
Hydrocortisone sodium succinate
Hydromorphone hydrochloride
Hydroxyzine hydrochloride
Ibandronate sodium
Ibutilide fumarate
Idarubicin hydrochloride
Idursulfase
Ifosfamide
Imiglucerase
Infliximab
Irinotecan hydrochloride
Iron dextran
Itraconazole
Ixabepilone
Kanamycin sulfate
Ketorolac tromethamine
Lanreotide acetate
Laronidase
Lepirudin recombinant
Leucovorin calcium
Leuprolide acetate
Levetiracetam
Levocarnitine
Levofloxacin
Levoleucovorin calcium
Lidocaine hydrochloride
Lincomycin hydrochloride
Linezolid
Lorazepam
Magnesium sulfate
Mechlorethamine hydrochloride
Medroxyprogesterone acetate
Melphalan hydrochloride
Meperidine hydrochloride
Mepivacaine hydrochloride
Meropenem
Mesna
Metaraminol bitartrate
Methadone hydrochloride
Methocarbamol
Methotrexate sodium
Methyldopate hydrochloride
Methylergonovine maleate
Methylprednisolone acetate
Metoclopramide hydrochloride
Micafungin sodium
Midazolam hydrochloride
Mitomycin
Mitoxantrone hydrochloride
Morphine sulfate
Moxifloxacin hydrochloride
Nalbuphine hydrochloride
Naloxone hydrochloride
Naltrexone
Nandrolone decanoate
Natalizumab
Nelarabine
Nesiritide recombinant
Octreotide acetate
Omalizumab
Ondansetron hydrochloride
Oprelvekin
Orphenadrine citrate
Oxacillin sodium
Oxaliplatin
Oxymorphone hydrochloride
Oxytetracycline hydrochloride
Oxytocin
Paclitaxel
Palifermin
Palonosetron hydrochloride
Pamidronate disodium
Panitumumab
Paricalcitol
Pegaspargase
Pegfilgrastim
Pemetrexed disodium
Penicillin g benzathine
Penicillin g potassium
Penicillin g procaine
Pentazocine lactate
Pentobarbital sodium
Pentostatin
Phentolaine
Phenytoin sodium
Phytonadione
Porfimer sodium
Potassium chloride
Pralidoxime chloride
Prednisolone acetate
Procainamide hydrochloride
Prochlorperazine edisylate
Progesterone
Promethazine hydrochloride
Propranolol hydrochloride
Protamine sulfate
Pyridoxine hydrochloride
Ranibizumab
Ranitidine hydrochloride
Rasburicase
Regadenoson
Reteplase
Rhophylac
Risperidone
Rituximab
Ropivacaine hydrochloride monohydrate
Sargramostim
Secretin synthetic human
Sincalide
Somatrem
Somatropin
Spectinomycin hydrochloride
Streptomycin sulfate
Streptozocin
Succinylcholine chloride
Sumatriptan succinate
Tacrolimus
Temsirolimus
Tenecteplase
Terbutaline sulfate
Teriparatide acetate
Testosterone
Testosterone cypionate
Testosterone enanthate
Testosterone propionate
Theophylline
Thiotepa
Thyrotropin
Tigecycline
Tinzaparin sodium
Tirofiban hydrochloride
Tobramycin sulfate
Topotecan hydrochloride
Torsemide
Trastuzumab
Triamcinolone acetonide
Triamcinolone hexacetonide
Trimethobenzamide hydrochloride
Trimetrexate glucuronate
Triptorelin pamoate
Urea
Urokinase
Vancomycin hydrochloride
Verteporfin
Vinblastine sulfate
Vincristine sulfate
Vinorelbine tartrate
Voriconazole
Ziconotide
Zidovudine
Ziprasidone mesylate
Zoledronic acid

Table 13: OLS and IV Estimates of the Effect on MMS on Shortage Days
Dependent variable: Shortage Days in a Year

	(1)	(2)	(3)	(4)	(5)	(6)
Off Patent	-5.549	-6.965	-26.63	-25.34	-9.513	-9.717
	(13.65)	(13.88)	(26.65)	(26.62)	(14.38)	(14.33)
Year $\geq$ 2005 $\times$ MMS	74.58**	130.8*				
	(35.12)	(70.40)				
Year $\geq$ 2005 $\times$ Log MMS			6.445*	9.090*	7.038***	8.406***
			(3.493)	(4.821)	(2.090)	(3.085)
Constant	17.62*		56.96**		27.60***	
	(9.403)		(23.81)		(10.53)	
Observations	3094	3094	1701	1701	2714	2714
# Drugs	308	308	152	152	244	244
R^2	0.169	0.167	0.223	0.222	0.193	0.193
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

Standard errors, in parentheses, are clustered at the drug level. Off patent is 15 years since earliest Orange Book approval. Columns (1) and (2) are the OLS and IV estimates using the IMS MMS in levels, rather than logs, as the treatment variable, respectively. Columns (3) and (4) use log of MMS again, but only include drugs whose median price is below the sample median drug price. Columns (5) and (6) only uses 2003 and 2004 to calculate the IMS MMS. Each regression contains molecule fixed effects and indicator variables for each year from 2002 to 2012.

Table 14: First Stage - MarketScan MMS on IMS MMS

	(1)	(2)	(3)
MMS	0.524***		
	(0.0430)		
Log MMS		1.153***	1.173***
		(0.0690)	(0.0569)
Constant	0.0242**	-1.319***	-0.922***
	(0.0102)	(0.272)	(0.209)
Observations	308	152	244
R^2	0.327	0.651	0.637
F-stat	148.6	279.3	425.1

Standard errors, in parentheses, are clustered at the drug level. First step in IVs, OLS of MarketScan MMS on IMS MMS. Column (1) runs both MMS measures in levels rather than logs. Column (2) is in logs, but only includes drugs whose median price is below the sample median drug price. Column (3) only uses 2003 and 2004 to calculate the IMS MMS.

Table 15: First Stage - Predicted MMS $\times$ Year $\geq$ 2005

	(1)	(2)	(3)
Off Patent	0.0129	-0.629**	-0.248
	(0.0123)	(0.251)	(0.200)
Predicted MMS	1.242***		
	(0.239)		
Predicted Log MMS		0.976***	1.062***
		(0.0599)	(0.0605)
Observations	3094	1701	2714
# Drugs	308	152	244
R^2	0.523	0.919	0.884
F-stat	16.42	161.1	134.9

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 14 interacted with ASP Reimbursement. Column (1) runs both MMS measures in levels rather than logs. Column (2) is in logs, but only includes drugs whose median price is below the sample median drug price. Column (3) only uses 2003 and 2004 to calculate the IMS MMS. Each regression also contains indicator variables for each year from 2002 to 2012, which are omitted from the table.

Table 16: 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	22.46	23.63	24.17	29.11*	16.27
	(16.40)	(20.51)	(20.57)	(17.49)	(19.37)
Log MMS	-2.073	-3.087	-3.229	-4.477	-3.865
	(1.873)	(2.064)	(2.077)	(3.053)	(3.520)
Log MMS $\times$ Off Patent	-4.785	-4.452	-4.321	-4.525	-8.832
	(3.440)	(4.477)	(4.493)	(5.542)	(6.355)
Year $\geq$ 2005	-1.218	2.079	0.746	1.349	0.195
	(9.679)	(10.32)	(10.38)	(9.840)	(10.82)
Year $\geq$ 2005 $\times$ Off Patent	65.31***	61.26***	62.65***	54.69***	74.20***
	(17.97)	(22.96)	(23.03)	(19.72)	(21.22)
Year $\geq$ 2005 $\times$ Log MMS	1.865	2.649	2.317	3.932	3.493
	(1.901)	(1.938)	(1.974)	(2.862)	(3.542)
Year $\geq$ 2005 $\times$ Log MMS $\times$ Off Patent	6.907*	5.952	6.297	6.417	12.98*
	(3.693)	(4.738)	(4.767)	(5.859)	(6.836)
Constant	11.77	7.538	6.945	8.580	10.20
	(9.246)	(9.921)	(9.965)	(9.488)	(10.34)
Observations	3094	3094	3094	3094	3094
# Drugs	308	308	308	308	308
R^2	0.0849	0.0846	0.0845	0.0834	0.0822
Drug Fixed Effect	No	No	No	No	No
Year Fixed Effect	No	No	No	No	No
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 earliest Orange Book 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. This table does not contain molecule fixed effects and indicator variables for each year.