NBER WORKING PAPER SERIES

MEDICARE REIMBURSEMENTS AND SHORTAGES OF STERILE INJECTABLE PHARMACEUTICALS

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Working Paper 17987
http://www.nber.org/papers/w17987

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
April 2012

I thank Ernst Berndt, John Beshears, Tim Bresnahan, Jeremy Bulow, Rob Chess, Jeffrey Clemens, Rena Conti, Liran Einav, Sherry Glied, Joshua Gottlieb, Rick Hornbeck, Mireille Jacobsen, Michael Link, Steve Mayer, Ted Okon, Michael Ostrovsky, Paul Oyer, Mar Reguant, Peter Reiss, Fiona Scott Morton, Robert Wilson, and Stefanos Zenios for comments. Special thanks to Lanier Benkard and Daniel Kessler who early on suggested theoretical mechanisms that are central to this paper. The views expressed herein are those of the author and do not necessarily reflect the views of the National Bureau of Economic Research.

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NBER Working Paper No. 17987
April 2012, Revised July 2012
JEL No. I11,I18,L51

ABSTRACT

This paper investigates the rise in shortages of sterile injectable pharmaceutical drugs in the US. I examine a policy change in 2005 that differentially reduced Medicare Part B payments for pharmaceuticals. Drugs that were subject to a greater policy change because they serve older patient populations have had greater increases in shortages. I interpret these results using a model of capacity choice with supply uncertainty. I conclude that Medicare's generous payments before the policy change provided manufacturers with incentives to invest in capacity or induced entry. The effect on total welfare of lowering payments is theoretically ambiguous.

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1 Introduction

This paper investigates the economic factors behind the marked recent rise of shortages of sterile injectable pharmaceutical drugs in the United States (Figure 1). Sterile injectable drugs include oncology drugs used in chemotherapy, anesthesia agents, and basic parenteral nutrition products like vitamins and electrolytes. They are mostly administered at a physician's office or in a hospital. Shortages cause doctors and patients to seek alternatives which are unfamiliar. When substitutes are poor, doctors and patients delay or forgo treatment which can be expensive and risky. The American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the American Society of Anesthesiologists (ASA) have all separetely 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)). Numerous popular press articles have reported on the impact of these shortages on patient outcomes (Hobson (2010), Rabin (2011)). Most of the drugs that have had shortages are off-patent, and traditionally have been readily available. Furthermore, increases of shortages for these drugs are not features of other developed countries' health systems. For these reasons, the rise in shortages of these drugs has bewildered patients and health care providers. This paper attributes the recent rise in shortages to a policy change that reduced reimbursements by Medicare to health service providers which administer these drugs.

The central message of this paper is that manufacturers take actions such as double sourcing ingredients, performing maintenance on manufacturing lines, and building new manufacturing lines that partially determine the likelihood of shortages. The extent to which manufacturers undertake these activities depends on the profitability of the drugs. I argue that the reduced Medicare reimbursements that took effect in 2005 lowered the profitability of this set of drugs. Empirically, I find that drugs that were more affected by the policy change have experienced a greater increase in shortages. I measure a drug's exposure to the policy change by the Medicare Market Share (MMS), as used by Duggan and Scott Morton (2010) to study the effect of introducing Medicare Part D. The MMS is the fraction of a drug's revenue that comes from Medicare patients. This relationship is quantitatively important. I estimate that a hypothetical generic sterile injectable

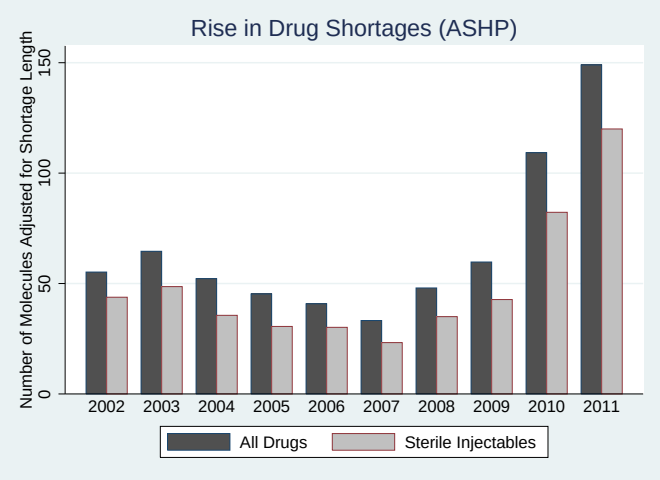

Figure 1: *The data for the chart are from the archives of the American Society of Health Pharmacists Drug Shortage web site. For each year, I check the number of months the drug is listed in shortage and divide by the number of months that are available to check (which is determined by how often the Internet Archive visited the site). The height of the bar for each year is equal to the sum of these fractions across active ingredient(s) and route of administration combinations.*

drug which served only Medicare patients experienced a 89.5 percentage point larger increase in shortages post-policy change than a hypothetical drug which served zero Medicare patients.

Payments by Medicare for drugs administered at a physician's office or in an outpatient setting at a hospital[1] dropped following the *Medicare Prescription Drug Improvement and Modernization Act* of 2003, commonly called the Medicare Modernization Act (MMA). This legislation is well known for creating the prescription drug benefit Medicare Part D. In addition to establishing Medicare Part D, the MMA changed the scheme via which Medicare reimburses for the purchase and administration of drugs in Part B which includes most sterile injectables. Before January 1, 2005, Medicare paid physicians and hospitals for these drugs proportional to their list price under a regime known as "Average Wholesale Price" (AWP) reimbursement. The AWP was not required to correspond to any actual transaction price. The AWP was often substantially higher than the actual transaction price[2]. A study by the Office of Inspector General found that the median percentage difference between AWP and Average Sales Price (ASP) was 50% (Office of Inspector General, 2005). Starting January 1, 2005, Medicare began to reimburse these drugs at 106% of the

[1] Administration of drugs in an outpatient setting at hospitals falls under Part B, while inpatient administration falls under Part A.

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

previous two quarter's ASP. This resulted in decreases on the order of 50% of reimbursements for these drugs to providers as seen in Figure 2. The reduction in payments was partially passed on to manufacturers as seen in Figure 3. The ASP regime is not a government price control, but rather cost-based reimbursement[3]. The ASP regime resulted in much less generous in payments than the previous AWP regime. I consider here whether the decrease in payments to providers affected manufacturers incentives to produce, install, and maintain capacity for these drugs, and conclude that it did.

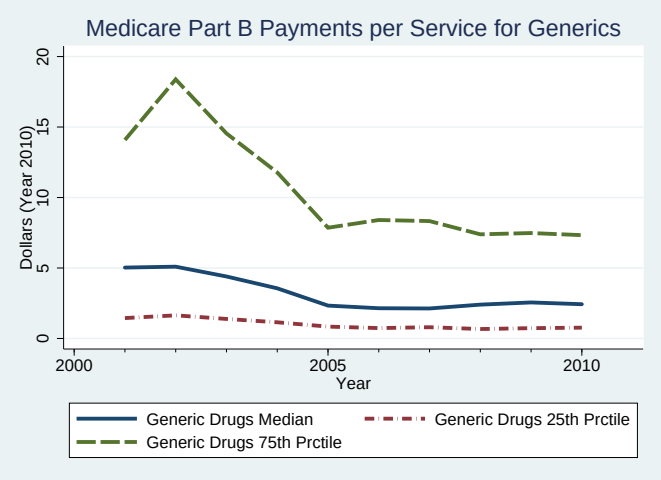

Figure 2: *From CMS Part B National Summary File. These lines represent the 25th, 50th, and 75th percentile of payments per service to health care providers by Medicare Part B for drugs in this paper's dataset. The majority of these drugs are non-biological sterile injectable drugs.*

Industry experts have pointed to this policy change as a potential culprit for rising shortages (Emmanuel, 2011). In testimony to the U.S. Senate Finance committee in December 2011, industry experts Scott Gottlieb, Rena Conti, and others pointed to decreased reimbursements from Medicare as contributing to drug shortages[4]. Senator Orrin Hatch released a draft legislative proposal in April

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

[4]In testimony to the U.S. Senate Finance Committee, Dr. Patrick Cobb of the Frontier Cancer Center and Blood Institute stated "As far as policy is concerned, I'm not really sure about legally how that would happen. But for us, we think that scrapping the ASP model for reimbursement for generic drugs is really important. The problem for us is that the ASP system for generic drugs has turned generic drugs into commodities. But the problem is that chemotherapy is not really a commodity. Because if you look at pork bellies, if you run out of pork chops, you can reasonably substitute a hamburger. But if you run out of Cytarabines, there are no substitutes for this. So chemotherapy has to be taken out of this commodity-based pricing that's the result of ASP. I think that's really important."

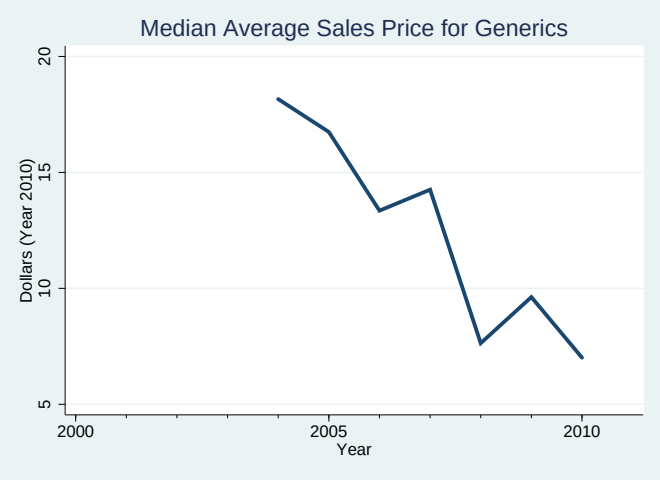

Figure 3: *From CMS. This line is the median Average Sales Price (ASP), weighted by number of services provided in 2004, for drugs in this paper's dataset. The ASP is the average transaction price paid by health care providers to manufacturers.*

2012 to address drug shortages by increasing payments by Medicare in certain circumstances.

There is not, however, consensus on whether the policy change is to blame for the increase in shortages. In the 370 page transcript of the Food and Drug Administration's (FDA) "Drug Shortage Workshop" held on September 26, 2011, Medicare payments were not mentioned once (Federal Drug Administration, 2011). President Obama issued an executive order on October 31, 2011 to address the problem of rising shortages. The executive order called for increased reporting by drug manufacturers facing supply issues and increased monitoring by the FDA, but does not mention payments or profitability of producing these drugs. A report by the U.S. Department of Health and Human Services (2011) discusses profitability and strategic behavior by manufacturers, but does not narrow in on Medicare reimbursements. Any alternative explanation would have to reconcile the empirical findings of this paper. For example, if increased FDA scrutiny were the culprit, it would have to be that the FDA increased scrutiny after the change to ASP reimbursement disproportionately on generic drugs which served more Medicare patients.

In related work examining the effect of the MMA on cancer treatment, Jacobson et al. (2010) find that patients with newly diagnosed lung cancer received more chemotherapy in 2006 than prior to the switch from AWP to ASP. Furthermore, these patients were treated more often with branded drugs rather than generic drugs. This finding is complementary to the empirical findings

in this paper as it reenforces that generic drugs became differentially more economically unappealing, however I do not model the margin of substitution amongst drugs. More broadly, health care spending has been increasing at a rate which many feel is unsustainable in the long term. However, cutting costs without regard to incentives to innovate and produce can lead to unintended consequences. This paper provides evidence that the reactions of manufacturers to reducing health care expenditures likely reduced capacity and maintenance investments, and resulted in an increase in shortages. As this paper deals with pharmaceuticals, it is most related to Finkelstein (2004) which found that increasing market size for vaccines through government policy is associated with increases in new vaccine development and clinical trials. This paper is also related to the effect of Medicare payments of provision of medical services. Cutler (1998) found mixed evidence on the effect of Medicare payment decreases in the 1980's and 1990's. More recently, Clemens and Gottlieb (2012) find that areas which had higher increases in Medicare reimbursements, after an administrative shift in 1997, experienced larger increases in care provision and health technology adoption.

As a theoretical framework, I use a model of manufacturers choosing capacity levels under supply uncertainty. I find that manufacturers will change their investments in capacity due to changes in downstream reimbursement for most parameter values. Competition sometimes leads to more shortages than a hypothetical social planner would choose. Competition decreases margins, therefore firms are more willing to tolerate stock outs when there is competition. Moving from generous reimbursement by Medicare to cost-based reimbursement as in the switch from AWP to ASP leads to lower capacity and more shortages. Furthermore, drugs which serve more Medicare patients experience a greater increase in shortages. Drugs with lower fixed costs of production also experience a greater increase in shortages. These two implications serve as the basis of the empirical work.

The main dependent variable in the empirical analysis is the fraction of time in year t that drug i[5] is under shortage. All the panel regressions condition on drug fixed effects, year fixed effects, and fixed effects for number of years since original approval. The first set of regressions interacts measures of Medicare Market Share (MMS) with an ASP-regulation dummy variable. The ASP-regulation variable is equal to one starting in 2005 when reimbursement switched from AWP to

[5]I define a drug as a combination of active ingredients and a route of administration.

ASP. MMS is based on the patient population of the conditions the drugs serve. Medicare predominantly covers elderly patients. If policy change reduced profitability of investing in capacity more for drugs which serve more Medicare patients, there should be a greater increase in shortages for higher MMS drugs. This strategy for identifying the effects of a Medicare pharmaceutical policy change was employed by Duggan and Scott Morton (2010) in their study of Medicare Part D. Since the MMS variable is measured with error, I use the moments of the age distribution of non-Medicare patients as instrumental variables for MMS. The IV coefficient estimates indicate the interaction of MMS and the ASP regulation dummy variable is both economically and statistically significant for off-patent drugs. The estimates imply that raising the MMS of a generic drug from zero to one hundred percent would increase shortage frequency 89.5 percentage points. The effect for on-patent drugs is not statistically distinguishable from zero. This is consistent with the theoretical framework in that on-patent drugs have higher prices than generics and therefore higher returns to capacity investment.

The model also predicts that drugs which have lower fixed costs relative to market size should have experienced a greater increase in shortages after switching from AWP to ASP based reimbursement. Under AWP, manufacturers facing more competitors should offer the largest discounts to health care providers. As the reimbursement rate under ASP takes into account discounts, reimbursement rates for these drugs dropped by more after the switch. I find that the interaction of the average number of manufacturers prior to the policy change with the ASP regulation dummy variable has a economically and statistically significant positive coefficient estimate. Drugs for whom there were more manufacturers prior to the policy change had greater decreases in payments and greater increases in shortages after the policy change.

Since the mechanism of reduced profitability operates through reduced Medicare payments, I next check whether there are more shortages for drugs which had a greater decrease in payments. I find that greater decreases in payments are associated with more shortages using the interaction of MMS and the ASP regulation dummy variable as an instrumental variable for payment levels. This covariance restriction isolates the variation in payments that can plausibly be attributed only to the policy change. The ultimate incentives facing a manufacturer depend on what fraction of payments to health providers[6] the manufacturer can capture. There is limited data on manufacturer's price

[6]These are the payments that were directly affected by the switch to ASP.

per drug prior to the policy change. However, the average sales price going to manufacturers is known after the policy change as that is the basis for ASP reimbursement. Furthermore, the data on average price was collected in the immediate two quarters prior to the policy change. This gives a two-quarter window into prices to manufacturers under the AWP regime. Drugs whose average sales price dropped differentially more due to the Medicare policy change had a greater increase in shortages.

Finally, I discuss potential solutions and why they might not have been implemented yet. I draw an analogy between sterile pharmaceuticals and electricity. Both markets share the features that supply and demand must be equated in fine time intervals and both have considerable uncertainty[7]. Electricity has dealt with these issues by creating extra incentives to produce when there is a danger of a shortage.

2 Institutional Background

Sterile injectable drugs are administered at a physician's office or a hospital. They are administered intravenously or intramuscularly and thus must be kept sterile. A typical generic sterile injectable drug is produced by three to four of the seven big generic manufacturers[8] in the U.S. A typical shortage occurs when a manufacturing line of one of the producers goes down. A line can go down because the manufacturer or the FDA identifies a quality issue[9] that could render the drug unsterile and requires that the issue be resolved, or because the manufacturer closes a facility or exits from producing a certain drug. Another reason shortages can occur is because of disruptions further up the supply chain. Manufacturers rely on producers of inputs such as Active Pharmaceutical Ingredients (API) whose supply can be disrupted due to natural disasters or manufacturing breakdowns. Once one manufacturer stops producing, it falls to the other manufacturers to make up the supply difference. However, the other manufacturers may not find it profitable to produce more of the drug, or may not be licensed to produce more of the drug, or may have been hit with the same supply shock as the first non-producing manufacturer.

[7] Sterile pharmaceuticals because of highly controlled manufacturing environments, and electricity because of weather.

[8] APP-Fresenius, Bedford-Ben Venue, Daiichi, Hospira, Sandoz, Teva, and West-Ward. Shortages have been occurring for several of these manufacturers as well as other smaller manufacturers.

[9] The FDA reports degradants such as bacterial/mold contamination, particles of foreign matter, glass, metal, or fibers in vials.

The supply chain for sterile injectable drugs is illustrated in Figure 4. Patients receive the drugs at hospitals or physicians' offices. Patients are usually insured either by the government through Medicare or Medicaid or by a private insurer. The insurer pays the health service provider at some price per administration of the drug. The health service provider buys the drugs from manufacturers through wholesale distributors. Hospitals often band together to form a group purchasing organization (GPO) which can negotiate volume discounts for buying drugs. The difference between the amount insurers reimburse for a drug and the price at which the health service provider buys the drug is the gross margin for the health service provider. Berndt (2002) provides a more general survey of the economics of pharmaceutical industry, while U.S. Department of Health and Human Services (2011) provides more detail on the sterile injectable portion of the industry.

The industry is highly regulated at all levels. Entry into producing a generic pharmaceutical requires submitting a request for approval to the FDA. To be approved, one must convince the FDA that their manufacturing process is sterile and follows good manufacturing practices. This process is described in Scott Morton (1999). Entry into branded drugs is also highly regulated, requiring a new molecule to demonstrate efficacy and safety compared to a placebo. Insurance is regulated by state insurance commissions and for a large number of individuals provided by the federal government via Medicare or by a combination of federal and state government via Medicaid.

2.1 The Policy Change: AWP to ASP

In 1992, Medicare declared that it would reimburse Part B drugs at Average Wholesale Price (AWP). However, "[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," (Medicare Payment Advisory Commission, 2003). In response to findings that Medicare's payment were well above acquisition costs for health providers, the reimbursement rate on these drugs was lowered to 95% of AWP in 1998. This decrease did not change that Medicare's payments were above acquisition cost. Medicare Payment Advisory Commission (2003) cite some egregious examples: Vincasar, a chemotherapy drug, had an AWP of $740, while being sold to physicians for $7.50. Berndt (2005) provides a detailed history of AWP. How AWP was chosen by manufacturers, given that it there was no formal basis, is unknown, and likely varied

by manufacturer. In theory, there was a strong incentive to raise AWP. In practice, the threat of regime change by CMS disciplined the AWP. In the theoretical model, I assume the AWP was set at the monopoly price.

In a well-intentioned effort to reduce Medicare costs, payments were lowered to 85% of AWP in 2004, and to 106% of the Average Sales Price (ASP) in 2005. 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 discounts and rebates. After the switch to ASP, payments to health providers for these drugs dropped, especially for generic drugs.

Shortages did not start increasing at large rates until 2009, four years after the policy change. However, the empirical analysis shows a larger increase in shortages for drugs with higher MMS starting in 2006. Second, in the years following Medicare's switch to ASP, a fraction of private payers also switched from AWP to ASP based reimbursement formulas, thereby further decreasing payments to providers for these drugs. According to (Mullen, 2007), for 2007, 21% of surveyed private payers planned to mimic ASP, while 76% intended to use rates above ASP or not use ASP at all. Industry observers also speculate that manufacturers found it profitable to keep producing old, less profitable drugs until new drugs came off patent. There was an increase in newly off-patent drugs beginning in 2007.

Some industry observers state that the switch from AWP to ASP can not logically be the cause of the increase in shortages as these payment levels are to providers and not manufacturers. The argument that payments to health providers dropped, but payments to manufacturers remained stable, does not account for the process by which manufacturers and health providers set prices. Empirically, one would ideally examine this with detailed data from manufacturers, but these data are so far kept confidential. However, in preparation for the switch to ASP, the Center for Medicare and Medicaid Services (CMS) collected average sales price data (ASP) for two quarters prior to the switch to ASP cost-based reimbursement. Average Sales Prices dropped in the in the period 2005-2010 compared with 2004 (Figure 3). Theoretically, furthermore, the payments made by Medicare to health providers form a large part of the surplus that manufacturers bargain over with health providers. When those payments drop, if manufacturers capture any surplus associated with their production, then the prices paid to manufacturers drop as well. Recent empirical research

on vertical relationships in other markets such as Crawford and Yurukoglu (2012) and Grennan (2012) reject the hypothesis of no market power on one side of a market with large firms on both sides.

3 Data

This study combines multiple data sources. Medicare Part B spending on drugs and Average Sales Prices comes from the Center for Medicare & Medicaid Services (CMS). Spending for a sample of private insurers on outpatient services comes from the MarketScan Commercial Claims and Encounters Database from Thomson Reuters (MarketScan). The incidence of shortages is from the American Society of Health System Pharmacists (ASHP). Finally, the Food and Drug Administration's (FDA) Orange Book provides the approved manufacturers and corresponding approval dates for drugs by year. I refer to a drug as a combination of an active ingredient and an administration route: intravenous or intramuscular injection, inhalant, oral or tablet, or topical. Some drugs are groups 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.

Medicare payments and services for the years 2000 to 2010 by Healthcare Common Procedure Coding System (HCPCS) code are from the Center for Medicare & Medicaid Services's (CMS) Part B National Summary File. 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 the 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. I adjust payments for inflation to year 2010 dollars. In the regressions to come, I cluster standard errors at the drug (that is, active ingredient plus route of administration) level. Depending on the regression, I either condition on drug fixed effects or HCPCS code fixed effects.

CMS also provides data on the Average Sales Price (ASP) by HCPCS code by quarter from 2005 to the present. The ASP is the quantity weighted average sales price accounting for discounts and rebates in the previous two quarters. The data for Q1 2005 provide a glimpse at payments manufacturers were receiving for two quarters under the AWP based reimbursement scheme.

Spending by non-Medicare patients is estimated from the MarketScan Commerical Claims and

Encounters database outpatient files. This data set has payments by year at the HCPCS code for a sample of self-insured employers and health systems. I use the years 2001-2009 to estimate the total non-Medicare spending, adjusted for inflation to year 2010 dollars, by active ingredient and route combination. From this measure, I create the variable Medicare Market Share (MMS) of drug i which is what fraction of a drug's revenue comes from Medicare patients. The MarketScan data is not, and does not claim to be, nationally representative of the private insurance market. The number of insured individuals rises from around five million in 2001 to 42 million in 2009. To create the estimate MMS for each year, I scale the revenue by drug as if the sample were nationally representative. For example, suppose there are 10 million individuals in a given year in the MarketScan data. I scale the revenue of each drug by the US population minus the number of individuals insured by Medicare and/or Medicaid divided by 10 million.

To assess whether the MMS variable I create is sensible, I check what diseases are served by the lowest MMS drugs and the highest MMS drugs. The highest MMS drugs are those inhalants which treat COPD and immunosuppressants used during organ transplantation. These make sense. The majority of organ transplants are kidney transplants, for which immunosuppressants are covered by Medicare Part B regardless of age. Many of the inhalants use nebulizers, a type of durable medical equipment, for administration. They also therefore fall under Medicare Part B. Other high MMS drugs include Pegaptanib Sodium, which treats age-related macular degeneration, and Triptorelin Pamoate, which treats prostate cancer. The lowest MMS drugs are Somatrem, a human growth hormone for children, Glatiramer Acetate, which treats multiple sclerosis, two drugs which treat hyper-thyroidism, and Urofollitropin, a fertility drug. The constructed MMS is positively correlated with the mean age of recipients of the drug in the MarketScan database, as one would require from a credible MMS measure.

The American Society of Health System Pharmacists (ASHP) maintains a website of current drug shortages. I accessed archives of this website on multiple dates per year going back to 2001. I create from this data a variable $shortages_{it}$ which indicates for what fraction of the dates I checked the archive website in year t is drug/route pair i indicated as being in shortage. The main weakness of this data is that it does not capture the varying magnitudes of shortages. The ASHP defines a shortage 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). This broad definition, however, is the best measure of shortages of which I am aware. I regress the logarithm of quantity of services by year in the MarketScan data on HCPCS code fixed effect, year fixed effects, years since earliest approval of the drug and the shortage variable. The estimated coefficient on the shortage variable ranges from -0.0962 with a standard error of 0.0914 (clustered at the drug level) in the sample of all drugs to -0.1974 with a clustered standard error of $.0920$ for the restricted sample of generic drugs. Therefore, the shortage measure is associated with fewer than average administrations of a drug. The mean value of the shortage variable across drugs which are always off-patent in the sample period is 0.1501. In the period of AWP based reimbursement (2001-2004), the mean is 0.1135, and in the period after the mean is 0.1713.

I use the Food and Drug Administration's Orange Book for the years 2001-2011 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[10] of a given drug in a given year. Since the analysis is at the drug level, I collapse the observations of a given drug into one observation per year. I separate drug-year combinations for drugs which have patent protection and those which don't by assuming any drug whose earliest approval is less than 18 years prior and has a maximum of one producers as being on patent. This definition is not exact, but the results of the paper are not sensitive to varying the threshold 18 from 15 to 20. The Orange Book does not track biological pharmaceuticals which are made by an organic process rather than chemical synthesis. The most famous biological is insulin. These drugs have a more complicated manufacturing process and have been subject to some shortages. Most biologicals are still on patent. This paper focuses on inorganic chemical compounds which make up the majority of administered drugs.

To combine these data sources, I begin with all HCPCS codes beginning with J ("HCPCS J Codes"), which indicates drug administration[11], in the period 2000 to 2010 that I observe in some year's Medicare Part B National Summary File. For each of the 690 observed unique HCPCS J

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

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

codes, I determine the relevant active ingredient(s) and route of administration by examining the HCPCS description and searching the FDA Orange Book when possible[12]. This leaves 496 unique HCPCS J codes whose active ingredient(s) and route of administration have a match in the FDA Orange Book. I join this set of drugs to the ASHP Shortage data by year, active ingredient(s), and route of administration, keeping all unmatched observations. If an observation from the matched set of drugs with HCPCS code J does not match to any shortage observation, I record that drug as not having shortages in the period of the sample. I join these data to the collapsed FDA Orange Book by active ingredient(s) and route of administration and year, keeping only matched observations. In addition to the HCPCS J code drugs which don't appear in the Orange Book[13], this excludes all the FDA Orange Book approval data for drugs which are never allocated an HCPCS code beginning with J[14]. Finally, I join these data to the Medicare payments from the Part B National Summary File by HCPCS code and year, average ASP by HCPCS code and year[15], and private payments from MarketScan data by HCPCS code and year. There are seventeen additional active ingredient(s) and route of administration combinations which never manifest in the MarketScan data. These are nearly all on patent at some point in the sample period, and so do not affect the major results of the paper[16].

4 Theoretical Framework

This section uses a model of entry and capacity choice with supply uncertainty to illustrate the change in production incentives and underlying welfare economics associated with changing reimbursement policies by Medicare. This class of models has been studied by Carlton (1978), Deneckere and Peck (1995), and Dana (2001) amongst others. The following presents results for two regimes: an no regulation regime and an Average Wholesale Price (AWP) regime. I associate the no regulation regime with the Average Sales Price (ASP) regulation that prevailed beginning in 2005. This analogy is appropriate because the ASP regime reimburses based on realized prices in

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

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

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

[15]Because of data availability, this matching is only for the years 2004 on.

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

the market[17]. The AWP regime features reimbursements for government insured patients at a price that is higher than what would normally be the acquisition price of the drug in some states of the world.

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 $\bar{p}$ 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 $\bar{p}$. If the total installed capacity is greater than the market size M, then the price of the good is zero.

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

Under AWP regulation, the government which reimburses hospitals at $\bar{p}$ no matter what the price the hospital purchased the medicine at when they serve Medicare patients[18]. The government purchases up to M_{gov} units at $\bar{p}$ no matter what total industry capacity turns out to be. Some fraction γ of that reimbursement rate will go to manufacturers. $\gamma \in [0, 1]$ represents a bargaining power parameter which is assumed to be the same across manufacturers.

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

Under ASP, manufacturer i solves:

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

[17]It is therefore not a regulated price. However, since 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.

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

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 regulation, 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[19]. I 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 payments 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.

I 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

[19]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.

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 regulation,

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

Analyzing this equilibrium condition analytically proved difficult even with strong distributional and functional form assumptions. I 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 with competition invests in additional capacity, it does not capture the social value of its investment, because competition drives average price below $\bar{p}$. In the other direction, when a firm invests in additional capacity, it imposes an externality on other firms by lowering average price. Furthermore, the government must raise the funds to pay for the AWP regulation, potentially distorting the decisions in some other area of the economy. Numerical simulations provide evidence that either effect can dominate, so the effect on total welfare is ambiguous.

The model's predictions for levels are not surprising. The AWP regulation 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 regulation 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 bun-

dled 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. It is unlikely that a credible such model would change the result that moving from AWP to ASP reimbursement would decrease incentives to invest in capacity, more so for drugs with more Medicare patients. 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.

5 Empirical Analysis

5.1 Shortages Conditional on Differential Exposure to Regulatory Change

I test whether the change in reimbursement by Medicare for drugs from AWP to ASP is associated with increased shortages. The change in policy occurred simultaneously for all drugs, therefore it is impossible to distinguish the effects of the policy change from a coincident change in the industry. The empirical strategy depends on the policy change affecting different drugs at varying levels as predicted by the model. As a first pass, I estimate the change in shortages as a function of a fifth order polynomial of a time trend and a dummy variable for the policy change ($ASPReg_t$ which is equal to one from year 2005 onward), drug, that is active ingredient(s) combined with route of administration, fixed effects (α_i) and dummy variables for each possible number of years since earliest approval ($Years\_since_{it}$).

$$Shortage_{it} = \alpha_i + \kappa Years\_since_{it} + \sum_{j=1}^{5} \delta_j t^j + \beta ASPReg_t + \epsilon_{it} \quad (1)$$

The results are in Table 2. In the sample of all drugs, the estimate of β is positive and economically significant, but statistically I can not reject that the true β is zero. Focusing on the sample of drugs which were off patent in 2001, the positive estimate of β is both economically and

statistically significant with a coefficient estimate of 0.1237 and a standard error of 0.0553. The effect does not exist for drugs which were on patent throughout the sample period. This is a theme throughout all the results. The effect of the policy change is on generic drugs. This is consistent with the model as on-patent drugs having high margins and strong incentives to invest in capacity and maintenance. This first result is suggestive that the post-policy change period had a marked increase in shortages for generics. However, the identification of this effect is partly an artifact of functional form assumptions. I next look more closely at which drugs had greater increases in shortages.

According to the model, the ASP regulation should increase shortages relatively more for drugs which derive a large fraction of their revenues from Medicare. I next estimate a regression of shortages on drug fixed effects, year fixed effects, a set of dummy variables for the years since earliest approval of the drug by the FDA, and an interaction of a dummy variable for the ASP Regulation period and the Medicare Market Share (MMS_i) of drug i.

$$Shortage_{it} = \alpha_i + \delta_t + \kappa Years\_since_{it} + \beta ASPReg_t MMS_i + \epsilon_{it} \quad (2)$$

The results are in Tables 3 and 4. In 3, the estimate of β in the sample of generic drugs is positive and economically significant, but can not reject zero as the true coefficient. The MMS variable is an estimate based on usage of these drugs in the MarketScan database. Under the assumption of classical measurement error, the coefficient on the interaction term, β, will be attenuated towards zero. I re-estimate the model using instrumental variables to eliminate the bias due to measurement error. I use moments of the age distribution of patients who receive the drug in the MarketScan database as a set of instruments for MMS. I then interact predicted MMS with the ASP regulation dummy variable[20]. Assuming the unobservable factors (ϵ_{it}) affecting shortages are unexpected supply shocks (plant breaks down) or demand shocks (new treatment approval), then the age distribution of patients receiving the drug should only correlate with shortages through its correlation with MMS. That is, these estimates are only credible if one is willing to assume that drugs which serve older patient populations did not have coincident and unrelated changes in their supply and

[20]I also directly use the interaction of the instrumental variables with the post-regulation dummy variable as instrumental variables for the interaction of MMS and the post-regulation dummy variable. The estimates are similar. I provide more detail in the robustness section.

demand conditions after the policy change. One potential confounding factor could be increased scrutiny by the FDA in the post-policy period on drugs which serve older patient populations, but this seems unlikely. In Table 4, the coefficient estimates change as theory would predict for classical measurement error. The coefficient estimate rises away from zero. The estimate is statistically significantly different from zero. Again, the effect is strongest for generic drugs, and does not seem to exist for drugs that are on patent throughout the sample. An increase in MMS of ten percentage points predicts a post-regulation increase in shortage frequency of around nine percentage points.

Lower fixed costs of production imply more producers of a drug, all else equal. More producers of a drug imply lower average prices in the ASP regime, and a greater increase of shortages when the government moves from AWP to ASP reimbursement. To measure fixed costs, I use the number of manufacturers producing the drug in the years 2001 to 2003. I also condition on the number of manufacturers approved for producing drug i in period t (Man_{it}).

$$Shortage_{it} = \alpha_i + \delta_t + \kappa Years\_since_{it} + \beta_1 ASPReg_t AvgMan_{i,2001-2003} + \beta_2 Man_{it} + \epsilon_{it} \quad (3)$$

The results are in Table 7. Drugs which had a higher average number of manufacturers producing the drug in 2001 to 2003 are associated with a greater increase in shortages in the post-policy change period, conditional on the number of manufacturers in the present. The results are both economically and statistically significant.

While MMS and fixed costs both predict differential impacts of the policy change, they do not measure the same conceptual object. The two variables are slightly positively correlated in the data because drugs serving more Medicare patients tend to serve more patients in general. Including both variables in the regression renders each variable statistically insignificant, however F-tests on their joint significance reject the null hypothesis of these variables jointly having no effect.

5.2 Shortages Conditional on Variation in Payments to Health Providers

The model predicts that the effect of the Medicare reduction in payments will decrease incentives to install capacity through reduced prices. I estimate whether there has been a greater increase in shortages for drugs with greater decreases in Medicare reimbursement rates that can be

attributed to the policy change. The specification is:

$$Shortage_{it} = \alpha_i + \delta_t + \kappa Years\_since_{it} + \beta_1 Payment\_per\_service_{it} + \beta_2 Man_{it} + \epsilon_{it} \quad (4)$$

Unobservable year-drug specific shocks to demand could affect payments and shortages simultaneously. To isolate the variation in payments due to the policy change, I use the interaction of predicted MMS and the ASP dummy variable as an instrumental variable for payments. The results in Table 10 are economically and statistically significant. I estimate that increasing payments by Medicare for generic drugs by ten percent would decrease the average frequency of shortages by 0.96 percentage points from a mean of 15.03%.

5.3 Shortages Conditional on Variation in Payments to Manufacturers

The previous subsection analyzed changes in shortage frequency with variation in payments to health care providers. The incentives of manufacturers depends on what portion of the payments to health care providers they are able to extract. Because the calculation of ASP relies on the payments by health care providers to manufacturers, one can observe an average payment to manufacturers by HCPCS code after the switch to ASP. Before ASP, we do not observe these payments except for a window of two quarters right before the switch to ASP, which was necessary to calculate the first ASP reimbursement rates. That is, for the first quarter of 2005, reimbursement rates were based on the average sales price from the third quarter of 2004, when the industry was under the AWP regime. The next regression looks at the difference in average shortage level before and after the change to ASP conditional on the difference of the average logarithm of ASP after the change and the logarithm of ASP in the two quarter window right before the change. The variation in the independent variable is in Figure 3.

$$\Delta Shortage_i = \beta_0 + \beta_1 \Delta log(ASP)_i + \epsilon_i \quad (5)$$

The coefficient estimate on β_1 is quantitatively important for generic drugs with a coefficient estimate of -0.2672, but because of the limited data, is only significant at the 90% confidence level with a standard error of 0.1590. It is likely that the change in ASP is an understatement of the true change for two reasons: first, the pre-ASP ASP is taken from two quarters prior to the switch

when the negotiating parties foresaw the coming change in reimbursement; second, CMS reduced payments to 85% of AWP from 95% of AWP in 2004 creating a minor drop in prices.

5.4 Exit Conditional on Differential Exposure to Regulatory Change

Some shortages are attributed to a manufacturer of a drug ceasing production and other manufacturers not being willing or able to ramp up production promptly. The next regression uses the number of manufacturers as a dependent variable. The effect of exogenously increasing the number of manufacturers of a drug on shortages is theoretically ambiguous because a smaller number of manufacturers will have higher margins, suggesting higher capacity, but, depending on the correlations of supply shocks across manufacturers, more manufacturers could imply higher total capacity. Nonetheless, I examine whether the policy change has been associated with exit from producing a drug.

$$Man_{it} = \alpha_i + \delta_t + \kappa Years\_since_{it} + \beta ASPReg_t MMS_i + \epsilon_{it} \quad (6)$$

The results in Table 9 show that the post-policy change decrease in the number of manufacturers is larger for drugs with higher MMS or when there were more manufacturers in the pre-policy change period. These estimates are not statistically very robust, however they suggest that the profitability of producing these drugs decreased after the Medicare payments dropped, so much so that some manufacturers stopped producing the drug altogether.

5.5 Robustness

5.5.1 Pre-existing Trends

If drugs with higher Medicare market shares were experiencing, for whatever reason, an increase in shortages prior to the policy change, then the estimates above might be capturing this trend, and one would not be justified in interpreting the coefficient estimate as evidence that the policy change has led to an increase in shortages. I assess whether such an effect exists by running the same specifications, but limiting the sample to 2001 to 2004, and considering 2003 and 2004 as a pseudo- "ASP Regulation" period. In the sample of always off patent drugs, the coefficient estimate for the interaction of predicted MMS and the pseudo-post-policy period, on the sample of off-patent drugs, is 0.1651 with a standard error 0.3987 compared to an estimate of 0.8951 and

standard error of 0.4255 on the true policy change interaction term.

I also carry out the regression of predicted MMS interacted with each year, excluding the base year of 2001. Table 6 shows that relative to 2001, higher MMS drugs were associated with lower shortages in 2002 and 2003, and higher thereafter. Strong pre-existing trends would predict that these coefficients should be positive and increasing by year. Between 2002 and 2004, there does exist an upwards trend in the coefficient estimates.

5.5.2 Instrumental Variables for Interaction Term

The interaction term $MMS*(Year \geq 2005)$ is measured with error, because MMS is measured with error. In the main results section, I estimate a cross sectional regression of MMS on the moments of the age distribution. I then interact the predicted MMS variable with the post regulation dummy. Here, I use the moments of the age distribution of non-Medicare patients as instrumental variables for this variable. The estimates are equivalent to estimation by two stage least squares. The predicted value of the interaction terms are non-zero and not equal from year to year in the pre-period because of other conditioning variables that vary from year to year. The coefficient estimate is 0.3530 with a standard error of 0.2823. It is therefore still quantitatively important, but not as large and not statistically significantly different from zero.

5.5.3 Instrumental Variable Relevance

I carry out a series of checks to avoid making incorrect inferences due to potentially weak instruments. First, the first stage regression coefficients make sense in that older age distributions are associated with higher raw MMS. It is hard to see this when using all the moments and functions of the moments as covariates, but a bivariate regression using only mean age produces a positive coefficient of .0041 and a standard error of .0017. The F-statistic from this bivariate regression is $F(1, 366) = 5.96$. Second, I run the instrumental variables regression by LIML rather than two stage least squares. I do this for the specification when I instrument directly for the interaction term, rather than interacting predicted MMS with the post-regulation dummy variable. The LIML results are nearly identical with a coefficient estimate of 0.3686 and a standard error of 0.3020.

6 Discussion

6.1 Alternative Explanations

As competing causes, others have suggested that increased scrutiny by the FDA, consolidation amongst manufacturers, grey market distributors, stockpiling by hospitals, and coincident exogenous shocks to the supply chain[21]. In theory, consolidation amongst manufacturers has ambiguous effects. Consolidation makes shortages less likely as consolidation increases market power and margins. However, depending on the covariance of shocks to manufacturing lines of different firms, consolidation could lead to increased shortages. Grey market distributors and stockpiling by hospitals have been documented at such low frequencies that they should be considered symptoms of shortages, rather than causes. While these explanations are *a priori* possible, the results in this paper suggest that they are unlikely because of the patterns of drugs which have increased shortages. For example, for increased FDA scrutiny or chance to be a valid competing hypothesis, it would have to be the case that the FDA increased scrutiny after the policy change disproportionately on generic drugs which served more Medicare patients or by chance supply shocks increased on generic drugs which serve more Medicare patients.

6.2 What is Special about Sterile Injectable Generic Pharmaceuticals?

Costly capacity and supply or demand uncertainty are features of many markets. For example, computer component manufacturing, aircraft manufacturing, and agriculture all share these characteristics. There are three additional characteristics that separate generic sterile injectables from these industries. First, supply and demand must match in fine time intervals. Consumption of most goods can be delayed without incurring too much cost. Health problems can get worse over time, so delaying is costly. Second, once there is more than one manufacturer of a drug, margins can drop dramatically because the producers are selling identical products. Third, storing sterile injectable pharmaceuticals is costly. They need to be kept sterile and can be sensitive to light and temperature. One industry which shares these extra characteristics is electricity generation. Electricity supply and demand must be in equilibrium at each instant to avoid power system failures. Electricity produced by different methods is identical for consumption purposes. Storing elec-

[21] On this latter suggestion, one of the maintained hypotheses of this paper is that manufacturers can take actions to increase the reliability of the supply chain if they find it profitable.

tricity by battery or with hydro-storage is currently considered prohibitively costly in most cases. The solution in electricity generation has been a mixture of rapid price adjustment and government regulation. Details on how electricity markets deal with shortages are in Cramton and Stoft (2005).

6.3 Options to Reduce Shortages

As mentioned in U.S. Department of Health and Human Services (2011), buyers of pharmaceuticals could sign contracts that impose penalties on manufacturers in cases of shortage[22]. This would increase average prices and increase the incentive to avoid stock outs by manufacturers. There are several possibilities for why those contracts haven't been implemented. One simple reason is lack of familiarity. Since shortages were not at a level of great concern prior to recent years, there was no need to develop such contracts. There may also be informational frictions when demand is privately known by health providers or when manufacturers can not observe all purchases that health providers make that prevent failure to supply clauses from emerging. Finally, it might not be in the incentive of any single manufacturer to sign such contracts unless all the other manufacturers do so as well.

Medicare could increase its payments to reduce shortages. The coefficient estimates here suggest that modest increases could have large effects on shortages. A more radical solution would be for Medicare to conduct a procurement auction for suppliers of the drug with heavy penalties in case of shortages. The FDA could theoretically condition approval to produce on maintaining sufficient levels of capacity, though this imposes a large burden on the regulator.

The model predicts that fewer shortages might not be socially optimal. While more detailed data would be helpful to study the question of total welfare, the model does predict that a monopoly firm will choose the socially optimal level of capacity. Patented drugs have fewer shortages in the data. This is suggestive that the socially optimal level of shortages is lower than what society experiences now for generic drugs, after the switch to ASP cost-based reimbursement.

7 Conclusion

I analyze how a change in Medicare's reimbursement scheme to cost based reimbursement lowered payments to health providers and likely played a role in the marked increase of shortages

[22]The report details that, while there exist "failure to supply" clauses currently, they usually contain language voiding the penalty in case of nationwide shortages.

of generic sterile injectable pharmaceuticals. Drugs that were more affected by the change in policy experienced a greater increase of shortages. The drugs that were more affected are drugs which treat diseases with older patient populations, because Medicare predominantly covers older patients. Also, drugs for which fixed costs are relatively low compared to market size were more affected because the policy change required payments by Medicare to depend on discounts made by manufacturers. When fixed costs are low, there are more manufacturers, more competition, and more discounts.

The key weaknesses of this paper are that the measure of shortages is coarse, and that the evidence on the margins going to manufacturers before the policy change is limited to two quarters before 2005. The measure of shortages does not measure how severe the shortages are. The measure I employ is useful, but could be improved upon by looking in greater detail at the individual shortages.

I observe payments by insurance providers to health care providers for administering these drugs for the years 2001-2010. I only observe how much of those payments go to the manufacturers from the health care providers for two quarters prior to the switch to ASP reimbursement. Based on this limited sample, drugs which had greater drops in payments to manufacturers after the policy change compared with the two quarters immediately before the policy change had greater increases in shortages. Further research using data from manufacturers, if made available, would be useful to further test the hypothesis of this paper using more data from the AWP period.

Further research on the details of how to increase incentives for manufacturers to produce these drugs would be useful. If Medicare were to increase its payments, then it faces the question of how high to increase its payments to ensure a stable supply without needlessly overspending. The design of contracts between manufacturers and health providers with penalty clauses to reduce shortages raises interesting theoretical questions. If payments are higher in shortage periods, then manufacturers have incentives to create artificial shortages. If health providers are able to multi-source drugs, then manufacturers who maintain more capacity and higher prices might find themselves with low market shares in non-shortage periods.

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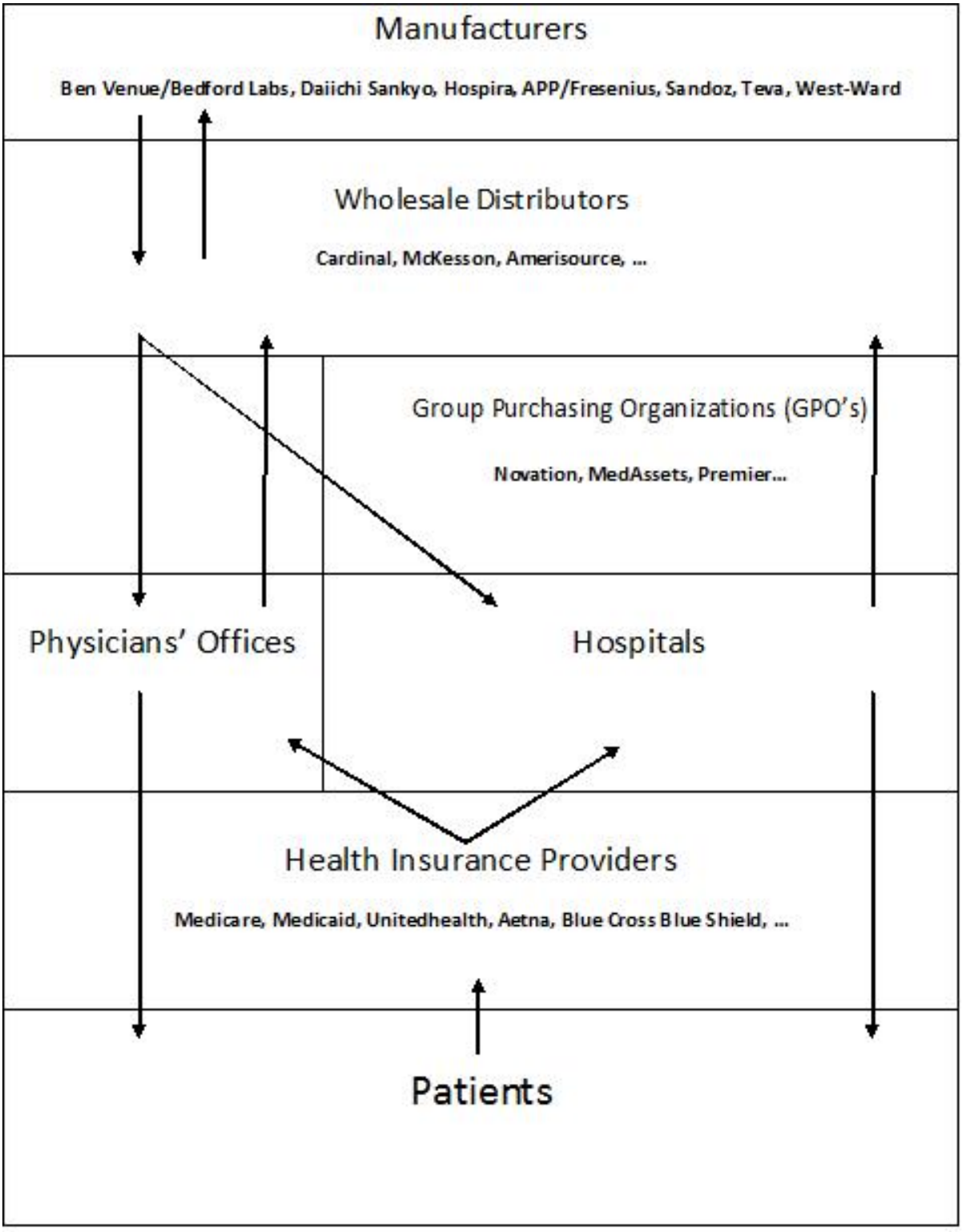

Figure 4: Supply chain of generic pharmaceuticals. Downward arrows are flows of products and services. Upward arrows are payments.

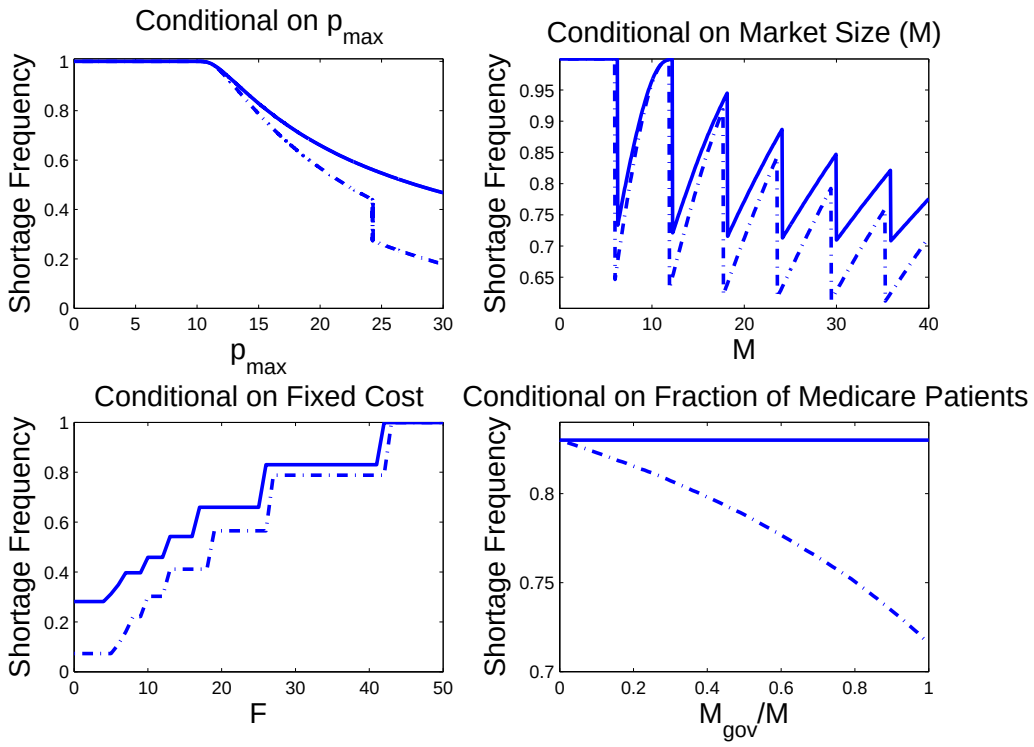

Figure 5: Model's predictions of shortage frequency as functions of model parameters. The solid lines are predictions for the cost-based ASP reimbursement regime. The dashed-dotted lines are predictions under the AWP reimbursement regime. Increasing p_{max} makes capacity investment more desirable and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

Table 1: Summary Statistics

	N	Mean	St. Dev.	Min	Max
Shortage Frequency	4917	0.0917	0.2508	0	1
Number of Manufacturers	4917	2.5678	2.6722	0	25
Always On Patent	4917	0.1747	0.3797	0	1
Always Off Patent	4917	0.4340	0.4957	0	1
Medicare Market Share (MMS)	4917	0.2211	0.2914	0	0.991589
Avg Number of Manufacturers in 2001-2003	4698	2.4105	2.4068	0	12
MedStat Age 25th Percentile	4917	35.3444	11.4969	2.4000	60.0000
MedStat Mean Age	4917	43.6412	8.0879	11.8437	60.0000
MedStat Median Age	4917	45.3958	9.2811	8.0000	60.1111
MedStat Age 75th Percentile	4917	53.4368	6.7498	14.8000	62.7778
MedStat Number of Services	3586	24433.3200	99863.5000	0.0000	1700000.0000
MedStat Payment Per Service	3584	410.8077	1265.3420	0.0000	19249.9500
Medicare Number of Services	3676	2801941	24900000	0	7.94E+08
Medicare Payment Per Service	3628	70.45084	481.6662	0	15520.77
Medicare Average Sales Price	2761	183.4932	1325.917	0.011	19345
Conditional on Always Off Patent					
Shortage Frequency	2134	0.1501	0.3064	0	1
Number of Manufacturers	2134	3.9405	2.4861	0	13
Medicare Market Share (MMS)	2134	0.1986	0.2697	0	0.983181
Avg Number of Manufacturers in 2001-2003	2134	4.2904	2.3918	1	12
MedStat Age 25th Percentile	2134	34.6319	11.0930	2.4000	52.2000
MedStat Mean Age	2134	43.5051	7.4395	12.8341	55.8006
MedStat Median Age	2134	45.5642	8.5545	8.7000	57.2000
MedStat Age 75th Percentile	2134	54.0894	5.8668	18.0500	61.2000
MedStat Number of Services	1647	38458.5100	129888.5000	1.0000	1700000.0000
MedStat Payment Per Service	1647	132.6307	342.8198	0.0000	3438.6940
Medicare Number of Services	1758	3683992	34300000	0	7.94E+08
Medicare Payment Per Service	1744	18.64804	64.59668	0	1269.378
Medicare Average Sales Price	1282	23.162	148.9453	0.011	2694.391
Conditional on Always On Patent					
Shortage Frequency	859	0.0081	0.0686	0	1
Number of Manufacturers	859	0.8976	0.3034	0	1
Medicare Market Share (MMS)	859	0.2362	0.2861	0	0.991589
Avg Number of Manufacturers in 2001-2003	662	0.7316	0.3445	0	1
MedStat Age 25th Percentile	859	39.9967	10.5737	12.0000	55.0000
MedStat Mean Age	859	46.4776	7.8132	17.5000	57.3892
MedStat Median Age	859	48.1692	8.6461	17.5000	60.1111
MedStat Age 75th Percentile	859	54.3654	6.9742	21.2500	62.7778
MedStat Number of Services	536	9096.6320	31767.5100	0.0000	280980.0000
MedStat Payment Per Service	534	1407.6750	2565.6750	0.0000	19249.9500
Medicare Number of Services	530	1676426	4686945.0000	0.0000	40100000
Medicare Payment Per Service	523	283.2202	1211.6750	0.0172	15520.77
Medicare Average Sales Price	565	704.2063	2849.6400	0.0180	19345

Table 2: Shortage Freq. Conditional on Time Trend Polynomial and Post-Regulation Dummy Variable

Dependent Variable:	Shortage Freq.	Shortage Freq.	Shortage Freq.
Year >= 2005 (ASP Regime)	0.0255 (0.0183)	0.1237 (0.0553)**	0.0051 (0.0100)
Years Since Earliest Approval Effects	Y	Y	Y
Ingredient - Route Dummy Variables	Y	Y	Y
Sample:	All	Always Off Patent	Always On Patent
R^2	0.0788	0.1602	0.0377
Number of Observations	3878	1430	807
Number of Drug-Route Clusters	368	130	88

Table 3: Shortage Freq. Conditional on Post-Regulation and Mis-measured MMS Interaction

Dependent Variable:	Shortage Freq.	Shortage Freq.	Shortage Freq.
Year >= 2005 * MMS Raw	0.0207 (0.0318)	0.0900 (0.0809)	0.0182 (0.0256)
Years Since Earliest Approval Effects	Y	Y	Y
Ingredient - Route Dummy Variables	Y	Y	Y
Sample:	All	Always Off Patent	Always On Patent
R^2	0.0796	0.1629	0.0400
Number of Observations	3878	1430	807
Number of Drug-Route Clusters	368	130	88

Table 4: IV Regression: Shortage Freq. Conditional on Post-Regulation and MMS Interaction

Year >= 2005 * MMS	0.2586 (0.1332)*	0.8951 (0.4255)**	0.1093 (0.1452)
Years Since Earliest Approval Effects	Y	Y	Y
Ingredient - Route Dummy Variables	Y	Y	Y
Sample:	All	Always Off Patent	Always On Patent
R^2	0.0811	0.1677	0.0426
IV:	Age Distribution	Age Distribution	Age Distribution
Number of Observations	3878	1430	807
Number of Drug-Route Clusters	368	130	88

Table 5: IV Regression: First Stage

Dependent Variable:	Ingredient-Route MMS	Ingredient-Route MMS	Ingredient-Route MMS
Constant	5.0386 (6.4147)	5.6036 (18.7044)	-0.5584 (35.3471)
Age25	-0.0240 (0.0200)	-0.1320 (0.0578)**	0.0455 (0.0435)
Mean Age	0.4181 (0.4181)	0.6206 (1.3110)	-0.0979 (1.9658)
Median Age	-0.0216 (0.0339)	-0.0230 (0.0923)	0.0081 (0.0808)
Age75	0.0850 (0.0422)**	-0.0472 (0.1259)	0.2314 (0.0928)**
Age25^2	0.0002 (0.0003)	0.0014 (0.0009)	-0.0007 (0.0006)
$(\text{Mean Age})^2$	-0.0066 (0.0065)	-0.0062 (0.0194)	-0.0011 (0.0272)
$(\text{Median Age})^2$	0.0005 (0.0004)	0.0006 (0.0011)	0.0002 (0.0009)
Age75^2	-0.0010 (0.0004)**	0.0000 (0.0013)	-0.0025 (0.0010)***
$(\text{Mean Age})^3$	0.0000 (0.0000)	0.0000 (0.0001)	0.0000 (0.0002)
log(Mean Age)	-4.0662 (4.2155)	-4.4124 (12.7036)	-0.7290 (21.2809)
Years Since Earliest Approval Effects	Cross-Section	Cross-Section	Cross-Section
Ingredient - Route Dummy Variables	Cross-Section	Cross-Section	Cross-Section
Sample:	All	Always Off Patent	Always On Patent
F Statistic	F(10, 357) = 3.40	F(10, 119) = 1.85	F(10, 77) = 2.55
Number of Observations	368	130	88

Table 6: Shortage Freq. Conditional on MMS - Year Interaction Terms

Dependent Variable:	MMS	MMS	MMS
Year = 2002 * MMS	-0.3234 (0.1357)**	-0.7222 (0.3403)**	-0.3293 (0.3425)
Year = 2003 * MMS	-0.1858 (0.1614)	-0.2283 (0.5328)	-0.2521 (0.2448)
Year = 2004 * MMS	0.0332 (0.1275)	0.0547 (0.4198)	-0.0643 (0.0569)
Year = 2005 * MMS	0.1208 (0.1430)	0.4015 (0.4649)	-0.0269 (0.0325)
Year = 2006 * MMS	0.1952 (0.1688)	0.6397 (0.6039)	-0.0114 (0.0297)
Year = 2007 * MMS	0.2043 (0.1410)	0.8351 (0.5376)	-0.0867 (0.0854)
Year = 2008 * MMS	0.1918 (0.1491)	0.6128 (0.4638)	-0.0310 (0.0342)
Year = 2009 * MMS	0.2439 (0.1763)	1.0965 (0.6161)*	-0.0059 (0.0357)
Year = 2010 * MMS	0.0506 (0.1984)	0.4909 (0.6065)	-0.0399 (0.0421)
Year = 2011 * MMS	0.0056 (0.2347)	0.6410 (0.7324)	-0.0897 (0.0899)
Years Since Earliest Approval Effects	Y	Y	Y
Ingredient - Route Dummy Variables	Y	Y	Y
Sample:	All	Always Off Patent	Always On Patent
R^2	0.0824	0.1699	0.0517
IV:	Age Distribution	Age Distribution	Age Distribution
Number of Observations	3878	1430	807
Number of Drug-Route Clusters	368	130	88

Table 7: Shortage Freq. Conditional on Number of Manufacturers in 2001 to 2003 and Number of Manufacturers

Dependent Variable:	Shortage Frequency	Shortage Frequency
Number of Mfctr_t	0.0088 (0.0051)*	-0.0104 (0.0126)
Year >= 2005 * Number of Mfctr 2001-2003	0.0206 (0.0054)***	0.0238 (0.0083)***
Years Since Earliest Approval Effects	Y	Y
Drug - Route Dummy Variables	Y	Y
Sample:	All	Always Off Patent
R^2	0.0931	0.1752
Number of Observations	3675	1430
Number of Drug-Route Clusters	336	130

Table 8: Shortage Freq. Conditional on MMS - Year and Avg 2001-2003 - Year Interaction Terms

Dependent Variable:	Shortage Frequency		
Year = 2002 * MMS	0.0123 (0.0107)	Year = 2002 * N01-03	-0.8131 (0.3484)**
Year = 2003 * MMS	-0.0017 (0.0105)	Year = 2003 * N01-03	-0.1963 (0.5330)
Year = 2004 * MMS	-0.0080 (0.0094)	Year = 2004 * N01-03	0.1195 (0.4317)
Year = 2005 * MMS	0.0091 (0.0108)	Year = 2005 * N01-03	0.2880 (0.4909)
Year = 2006 * MMS	0.0089 (0.0116)	Year = 2006 * N01-03	0.5155 (0.6307)
Year = 2007 * MMS	0.0043 (0.0111)	Year = 2007 * N01-03	0.7579 (0.5506)
Year = 2008 * MMS	0.0101 (0.0090)	Year = 2008 * N01-03	0.4899 (0.4758)
Year = 2009 * MMS	0.0163 (0.0100)	Year = 2009 * N01-03	0.9145 (0.6279)
Year = 2010 * MMS	0.0463 (0.0128)***	Year = 2010 * N01-03	0.0401 (0.6388)
Year = 2011 * MMS	0.0645 (0.0144)***	Year = 2011 * N01-03	0.0304 (0.7111)
Number of Mfctr_t	-0.0068 (0.0129)		
Years Since Earliest Approval Effects	Y		
Ingredient - Route Dummy Variables	Y		
Sample:	Always Off Patent		
R^2	0.2057		
IV:	Age Distribution		
Number of Observations	1430		
Number of Drug-Route Clusters	130		

Table 9: Number of Manufacturers Conditional on Post-Regulation and MMS Interaction

Dependent Variable:	N	log(N)	N	log(N)	N	log(N)
Year >= 2005 * MMS	-2.6508 (2.4601)	-0.5068 (0.5068)			-1.0272 (2.2724)	-0.2506 (0.5020)
Year >= 2005 * Num Mfctr 2001-2003			-0.1895 (0.0445)***	-0.0331 (0.0108)***	-0.1859 (0.0454)***	-0.0323 (0.0112)***
Years Since Earliest Approval Effects	Y	Y	Y	Y	Y	Y
Drug - Route Dummy Variables	Y	Y	Y	Y	Y	Y
Sample:	Always Off	Always Off	Always Off	Always Off	Always Off	Always Off
R^2	0.1207	0.0817	0.1686	0.1034	0.1692	0.1040
IV:	None	None	None	None	Age Distribution	Age Distribution
Number of Observations	1430	1381	1430	1381	1430	1381
Number of Drug-Route Clusters	130	130	130	130	130	130

Table 10: OLS and IV Estimates of Shortage Freq. Conditional on Medicare Payment per Service

Dependent Variable:	Shortage Frequency	Shortage Frequency	Shortage Frequency	Shortage Frequency
Payment Per Service	-0.0005 (0.0003)*	.	-0.0035 (0.0019)*	.
log(Payment Per Service)	.	-0.0669 (0.0182)***	.	-0.0966 (0.0489)**
Number of Mfctr_t	-0.0124 (0.0192)	-0.0114 (0.0173)	-0.0181 (0.0187)	-0.0114 (0.0154)
Years Since Earliest Approval Effects	Y	Y	Y	Y
HCPCS Code Dummy Variables	Y	Y	Y	Y
Sample:	Always Off Patent	Always Off Patent	Always Off Patent	Always Off Patent
IV:	None	None	MMS*(Year>=2005), Num0103*(Year>=2005)	MMS*(Year>=2005), Num0103*(Year>=2005)
Number of Observations	1744	1743	1744	1743
Number of Drug-Route Clusters	129	129	129	129

Table 11: IV First Stage: Medicare Payment per Service on MMS and Number of Manufacturers 2001-2003 Interacted with (Year $\geq$ 2005)

Dependent Variable:	Payment Per Service	log(Payment Per Service)
Year >= 2005 * MMS	-348.0184 (207.3301)*	-1.3261 (1.9913)
Year >= 2005 * Number of Mfctr 2001-2003	-2.4199 (1.4813)	-0.2037 (0.0438)***
Number of Mfctr_t	-3.2717 (1.4886)**	-0.0638 (0.0454)
Years Since Earliest Approval Effects	Y	Y
HCPCS Code Dummy Variables	Y	Y
Sample:	Always Off Patent	Always Off Patent
F-Statistic	F(1, 128) = 2.93	F(1, 128) = 0.97
Number of Observations	1744	1743
Number of Drug-Route Clusters	129	129

Table 12: OLS and IV Estimates of Change in Shortage Frequency on Change in log(ASP)

Dependent Variable:	Δ Shortage	Δ Shortage
Change in log(ASP)	-0.0216 (0.0337)	-0.2672 (0.1590)*
Years Since Earliest Approval Effects	Cross Section	Cross Section
HCPCS Code Dummy Variables	Cross Section	Cross Section
Sample:	Always Off Patent	Always Off Patent
IV	None	Predicted MMS
Number of Observations	119	119