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SPECIALTY DRUG PRICES AND UTILIZATION AFTER LOSS OF U.S. PATENT EXCLUSIVITY, 2001-2007

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ABSTRACT

We examine the impact of loss of U.S. patent exclusivity (LOE) on the prices and utilization of specialty drugs between 2001 and 2007. We limit our empirical cohort to drugs commonly used to treat cancer and base our analyses on nationally representative data from IMS Health. We begin by describing the average number of manufacturers entering specialty drugs following LOE. We observe the number of manufacturers entering the production of newly generic specialty drugs ranges between two and five per molecule in the years following LOE, which is generally less than that observed historically for non-specialty drugs. However, the existence of time-varying and unobservable contract manufacturing practices complicates the definition of "manufacturers" entering this market. We use pooled time series methods to examine whether the neoclassical relationship between price declines and volume increases upon LOE holds among these drugs. First, we examine the extent to which estimated prices of these drug undergoing LOE fall with generic entry. Second, we estimate reduced form random effects models of utilization subsequent to LOE. We observe substantial price erosion after generic entry; average monthly price declines appear to be larger among physician-administered drugs (38-46.4%) compared to oral drugs (25-26%). Additionally, we find average prices for drugs produced by branded manufacturers rise and prices for drugs produced by generic manufacturers fall upon LOE. The latter effect is particularly large among oral drugs. In pooled models, volume appears to increase following generic entry, but this result appears to be largely driven by oral drugs. We discuss second-best welfare consequences of these results.

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SECTION 1: INTRODUCTION

We examine the impact of generic entry on the prices and utilization of prescription drugs between 2001 and 2007 in the United States (U.S.). Whereas previous research on the impact of loss of exclusivity (LOE) on entry patterns and use trends following the enactment of the 1984 Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Act") has focused primarily on self-administered oral and tablet/capsule formulations dispensed through the retail pharmacy sector, here we focus on specialty drugs. Although there is no universally accepted definition of specialty drugs, typically they fall into at least one of several categories: They are physician-administered parenterally or self-administered by patients through injection, inhalation or another non-oral method; they require specialized knowledge or manufacturing processes to reliably and reproducibly manufacture; they entail specialty distribution channels rather than retail pharmacies; they are covered under the outpatient medical benefit of public and private insurers rather than the pharmacy benefit; and when patent-protected are said to have "high prices". Among those categories, here we limit our empirical cohort to specialty drugs commonly used to treat cancer, and base our analyses on nationally representative data from IMS Health on monthly volume and inflation-adjusted sales revenues. This empirical focus is relevant both to researchers and policy makers. While the market for producing cancer drugs is small compared to that of all prescription drug manufacturing, specialty drug use is an important driver of current national prescription drug spending levels and trends (Aitken, Berndt, Cutler 2011; GAO 2013). The potential impact on national spending levels and trends among high-price and high-revenue cancer and other specialty drugs expected to undergo LOE is the subject of significant policy interest (U.S. Department of Health And Human Services OIG 2011; Conti et al. 2013).

Among pharmaceuticals, LOE opens a drug up to potential competition from multiple manufacturers previously limited to the sole "branded" producer. Price and utilization of drugs post-LOE have been studied extensively among non-specialty drugs (Caves et al. 1991; Grabowski, Vernon 1992, 1996; Frank, Salkever 1997; Wiggins, Maness 2004; Reiffen, Ward 2005; Berndt et al. 2003). Our paper contributes to this literature by documenting the average number of manufacturers entering specialty drugs undergoing LOE in the first year after patent expiration and thereafter, and by comparing raw counts of generic manufacturer entrants to those observed among studies of specialty and non-specialty drugs in a contemporaneous cohort (Scott-Morton 1999, 2000). However, we do not derive welfare implications from these entry count results. Our review of the organization of specialty drug production literature suggests the substantial presence of time-varying and unobservable contract manufacturing practices seriously complicates and may even obviate the definition of unique "manufacturers" entering this market.

Rather, using pooled cross-sectional and time series methods, we engage in a three-step

examination of whether the neoclassical relationship between presumed price declines upon LOE and volume increases holds among these drugs. First, we examine the extent to which estimated manufacturer prices of the drugs undergoing LOE fall with generic entry among oral and physician-administered (injected and/or infused) drug formulations. Second, we document raw trends in inflation-adjusted sales revenues and utilization following initial LOE. Third, we estimate reduced form random effects models of utilization subsequent to LOE, accounting for molecule formulation and therapeutic class and entry patterns (Wiggins, Maness 2004). We discuss second-best welfare consequences of these estimated price and use results, after acknowledging the presence of complications to first-best welfare calculations in this market.

SECTION 2: UNIQUE INSTITUTIONS GOVERNING GENERIC ENTRY, MANUFACTURING AND PRICING OF SPECIALTY DRUGS

In this section, we review unique aspects of the supply and demand for specialty drugs. This discussion is not meant to be exhaustive, but rather is intended to provide sufficient context to motivate our empirical approach and lay the foundation for the interpretation and discussion of our findings.

Branded and generic drug regulatory approval. Analyses of prescription drug markets distinguish two types of drugs. Brand name ("pioneer") drugs are approved for use in a given indication by the FDA under New Drug Applications (NDAs) submitted by manufacturers typically based on the results of several phase III randomized controlled clinical trials. These pioneering manufacturers are able to sell their products exclusively while the drug is patent protected. In anticipation of patent expiration and any other loss of exclusivity, other manufacturers apply to the FDA to obtain approval to market the "generic" drug under an Abbreviated New Drug Application (ANDA).

FDA approval of an ANDA does not require its manufacturer to repeat clinical or animal research on active ingredients or finished dosage forms already found to be safe and effective. Rather, to gain approval the manufacturer submitting the ANDA must only establish that the generic contains the same active ingredients; be identical in strength, dosage form, and route of administration; be bioequivalent; and be manufactured under the same strict standards as the brand-name pioneer drug. When submitting an ANDA, the manufacturer provides evidence either substantiating bioequivalence and compliance with current good manufacturing practices (cGMP) at its own manufacturing sites, or else indicates that portions of the manufacturing (such as production of active pharmaceutical ingredients (APIs) or final fill and finish production) will be outsourced to another supplier or contract manufacturing organization (CMO). The FDA is responsible for enforcing ANDA requirements and current cGMP standards among generic manufacturers both upon entry and via subsequent periodic routine inspections. Production

facilities may be inspected and certified post-approval to verify they meet FDA requirements, including in particular specific lines, vats and batches; typically inspections occur every 18-36 months per facility. For oral tablets and capsules, the direct costs of ANDA applications are modest ($1-$5M) compared to potential profitability (Berndt, Newhouse 2013). Not much is known regarding the direct costs of obtaining ANDA approvals among infused or injected drugs.

Supply conditions. What is known is that the manufacturing technology involved in the production of infused or injected drugs is highly specialized. Sterility is particularly important for these drugs, providing the primary challenge related to their manufacturing, packaging and distribution. Sterile production requires keeping human operator intervention to a minimum, accomplished by separating or removing highly trained and skilled employees from the aseptic clean air and water environment. Contamination can involve pathogens, fragments of vial rubber stoppers and broken glass. Because manual steps create opportunities for contamination, automated processes for the filling and finishing of these products are desirable. Unlike most capsules and tablets, liquid APIs are the base materials for production of these drugs. Risk of contamination is also important in the sourcing of API. API is typically sterilized using filtration, with the sterile product then held in an aseptic storage tank until it is used for final "fill and finish" ANDA production.

An implication is that even though regulatory barriers to entry among manufacturers of these drugs are likely rather modest, the small market size and high fixed and variable production costs of at least some specialty drugs likely results in modest entry post-LOE, with production being concentrated among specialized manufacturers. Evidence in support of this market characterization is derived from multiple sources. From industry sources, it is clear manufacturers with noted current commitments to the production of specialized injected or infused drugs for the domestic market include Hospira, Teva Pharmaceuticals and Teva Parenteral ME, Baxter and Fresenius (APP) (EMD Serono 2013; PBMI 2014). Furthermore, only a handful of injected or infused generic drug manufacturers produce their own liquid or lyophilized API (Teva, Sandoz, Watson) with the remaining manufacturers acquiring it from non-affiliated producers. Adding some measure of confidence to our characterization, we note these observations are consistent with previous empirical work on generic entry into these markets, suggesting the mean number of approved ANDA manufacturers of injected or infused specialty drugs ranges between 2 and 5, compared to the 5-15 ANDA manufacturers of oral drugs undergoing LOE 1984-1994 in the U.S. (Scott-Morton 1999, 2000; Aitken et al. 2013) and among oral drugs undergoing LOE in Japan 2004-2006 (Iizuka 2009).

Another important characteristic of the market for injected or infused drugs is that a number of prominent manufacturers hold ANDAs for their own drugs and simultaneously act as contract manufacturers for others (e.g., Hospira, Boehringer Ingelheim, Luitpold, Fresenius/APP, West-Ward)

(FDA 2011; Conti 2014). For example, one notable manufacturer of many generic injectable drugs, Ben Venue, was (until very recently) the CMO subsidiary of Boehringer Ingelheim of Germany. There are likely significant cost efficiencies gained from outsourcing the production of injected or infused drugs to established CMOs. To the extent that they are able to exploit economies of scope and scale, CMOs can offer their services at a cost lower than that incurred by self-manufacturing. Moreover, because of scope economies, CMOs face incentives to expand the portfolio of products they produce, but they can also take advantage of scale economies, producing the same injected or infused drug for different ANDA manufacturers (Macher, Nickerson 2006). A recent report (FDA 2011) documents more than a doubling of manufacturers relying on CMOs among branded and generic drugs worldwide 2001-2010. Yet, these statistics require independent verification. The FDA does not make public a list of which CMOs manufacture a given drug. As far as we are aware, this information is not made available publicly by any other regulatory agency nor by any private data vendor. Thus, the importance of contract manufacturing for drugs supplied to the U.S. market generally (both specialty and non-specialty) and our sample of drugs specifically is unobservable by researchers, stakeholders and regulators. This point fundamentally casts doubt on the validity of simple manufacturer counts, as well as on the interpretation of manufacturing count entry models of any and all generic drugs, and has further implications for policy makers charged with monitoring competition in this market.

Information and Regulatory Timing. The FDA does not publicly reveal when it receives an ANDA, nor the identity of its applicant. In this sense, the limited information regarding the entry process is symmetric and simultaneous among potential applicants. However, manufacturer officials might announce their entry plans to inform their shareholders. Scott-Morton (1999) suggests such announcements may be used to deter other competitors from entering the market. Although a manufacturer may announce its intentions to enter the supply of a particular molecule for the domestic market, there is no guarantee that FDA approval will be granted in the time frame anticipated by the applicant. Consequently, a manufacturer who submits an ANDA cannot generally credibly commit to a market with its application announcement alone.

Supporting this view, a review of recent trends suggests the timing of ANDA approval has become more variable for applicants 2001-2011 and, consequently, less predictable (Parexel 2013). While the number of original total ANDA approvals has increased substantially, from 132 in 2001, 392 in 2007, to 422 in 2011, the number of original injectable ANDA approvals also increased from 32 in 2001 (24.2% of total), 64 in 2007 (16.3% of total), to 88 in 2011 (21% of total). Mean (median) FDA ANDA review times initially fell from 21.1 (18.1) months in 2001 to 19.9 (15.7) months in 2004, but then increased to 21.4 (18.9) months in 2007 and 32.9 (29.5) months in 2011. The number of backlogged pending ANDAs under FDA review increased sharply during this period, from 374 in 2001 to 615 in 2004, 1,309 in 2007

and 2,693 in 2011.

Entrant terminology. In light of this transparency concern, it is important to define an "entrant" into a generic drug market segment after LOE using the terminology conventions of the FDA. A "sponsor" is a firm who submits a new drug application (NDA) for a branded small molecule drug or a biologics license application (BLA) for a novel, branded biological-based drug, or an ANDA. An application holder is a firm who "holds" the NDA, BLA or ANDA; "sponsors" become "application holders" once the application is approved by the FDA. "Manufacturers" are companies that produce the NDA, BLA, or ANDA. It is possible for the manufacturer to not be the "application holder" in the event that manufacturing of the drug is contracted out to another vendor.

When a NDA, BLA or ANDA is approved by the FDA it is assigned a unique, three-segment number, the "National Drug Code (NDC)", which serves as a universal product identifier for drugs, based on The Drug Listing Act of 1972.[1] The FDA publishes the listed NDC numbers and the information submitted as part of the daily updated listing information in the NDC Directory. The manufacturer identified in the NDC, is called the "NDC labeler". The NDC labeler can be the NDA, BLA or ANDA application holder, the contract manufacturer, the repackager, or the compounder of the drug.

Given available data and transparency concerns discussed above, our operative definition of generic "manufacturer" after LOE is the drug's "labeler" excluding repackagers. We describe how we identify and exclude repackagers in the empirical methods section.

Drug Shortages. Since 2006, the U.S. has experienced a marked increase in prescription drug shortages. Three-quarters of shorted drugs in 2011 were sterile injectable products, such as chemotherapy, anesthesia and anti-infective agents (U.S. Department Of Health And Human Services, ASPE 2011; Woodcock, Wosinska 2013) and over 80% had lost patent protection, experienced generic entry and consequently were (in theory) multi-sourced by competing generic drug manufacturers. The majority of generic specialty drug shortages initially appeared around 2009 and thereafter. These shortages have raised considerable alarm since the welfare consequences for pediatric cancers and discontinuation of clinical trials are presumed to be disproportionately high (Gatesman, Smith 2011; Wilson 2012). The University of Utah Drug Information Service (UUDIS) tracks the number of shortages at the end of each quarter. Recently they reported that over the past five quarters the number of shortages was at the highest level since the beginning of 2010. This growth is primarily due to the unusual persistence of existing shortages rather than growth in the number of new shortages (Goldberg 2013).

The proximal causes of most domestic drug shortages are also clear. Beginning around 2009-2011, routine FDA certification inspections uncovered significant lapses in maintenance of facilities that

[1] See Section 510 of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 360.

produce the fill and finished dosage of the drug among many manufacturers (Woodcock, Wosinska 2013). Various inspections investigating suspected lapses in manufacturing practices resulted in the closure of other "fill and finish" facilities (Ben Venue and American Regent in 2010 and Ranbaxy in 2014) and API manufacturers (Ranbaxy in 2014). Current policy efforts to mitigate shortages have largely focused on improving the FDA's capabilities to respond to the crises (FDA 2013).

Supply and demand side prices. Among physician-administered injected and infused specialty drugs, the acquisition price of the drug paid by the provider (the price received by the supplying manufacturer – "supplier prices") may differ substantially from the insurer reimbursement received by the provider ("demand side" prices). This divergence is largely due to Medicare and commercial insurers' reimbursement policies that imperfectly reflect these drugs' actual acquisition costs.

On acquisition prices, NDA, BLA and ANDA (and in some cases, drug catalog publishers) set the wholesale acquisition cost (WAC) of a given drug. Wholesalers, retail pharmacies and other purchasers generally acquire branded drugs from manufacturers at a modest discount off WAC (commonly a 1-2% prompt payment discount); generic drugs are typically discounted much more heavily off of WAC. Additional discounts from wholesalers or from manufacturers negotiated by retail pharmacies, by pharmacy benefit managers (PBMs) or by group purchasing organizations (GPOs) on behalf of their members may be directly related to a purchaser's volume or share of a drug within a therapeutic class and also over a bundle of drugs (Frank 2001). ANDA manufacturers of oral drugs can compete intensively on price to win GPO or PBM contracts. Generally, orally formulated anti-cancer and selected other specialty drugs are less prone than others to these acquisition price negotiations because of the lack of perceived therapeutic substitutes (EMD Serono 2013; PBMI 2014). Physician-administered infused and/or injected drugs may not be prone to acquisition cost discounts related to preferred formulary and/or copayment status arrangements at all, but may be subject to volume based purchaser discounts. In addition, purchasers of specialty oral and injected/infused drugs can be eligible for federally mandated "best price" rebates off average manufacturers' price (AMP) for Medicaid insured patients, similar to non-specialty drugs. AMP is essentially the average price wholesalers and certain pharmacies pay for drugs distributed to retail community pharmacies (U.S. Department of Health and Human Services OIG 2010).

Qualified outpatient hospital-based clinics, affiliated community-based clinics and contract pharmacies are also able to purchase oral and injected/infused drugs directly from manufacturers or wholesalers (but not via GPOs) at the federally mandated 340B discounted price off AMP. 340B prices for branded drugs must be at least 23.1% discounted off of the AMP, but actual negotiated 340B prices are frequently lower than the 340B ceiling price (GAO 2011). Consequently, discounts through the 340B program have become a prominent part of supplier prices in the specialty and non-specialty drug market.

A recent analysis by Drugchannels.com (2014) suggests drug purchases under the 340B drug discount program have grown by 800%, from $0.8 billion in 2004 to $7.2 billion in 2013. In 2013, hospitals received 340B discounts on at least 25% of their drug purchases, compared with only 3% in 2004.

Insurers reimburse the use of the specialty drugs in two ways: via the pharmacy benefit (oral specialty drugs, similar to that of non-specialty oral drugs) or the outpatient medical benefit (all physician-administered injected and infused drugs and a small number of oral drugs). Commercial insurers also provide coverage for Medicare insured individuals obtaining drugs covered under the pharmacy benefit ("Part D"). Commercial insurers that provide Part D coverage for prescription drugs are required to cover all drugs in six protected classes, one of which is anticancer drugs. This protection requires commercial insurers to offer pharmacy benefits to Medicare beneficiaries that includes all available anti-cancer drugs, with limited supply side access controls. Reimbursement for pharmacy benefit covered drugs is generally considered to reflect acquisition costs (albeit imperfectly), other than the discounts obtained through the 340B program (PBMI 2014).

Medicare, the public insurance program providing virtually universal coverage to adults age 65 and older, is the most prominent payer for drugs covered under the outpatient medical benefit ("Part B") (i.e. largely infused and/or injected specialty), followed by commercial insurers and then state Medicaid agencies (MedPAC 2006). By law, neither Medicare nor Medicaid can consider drugs' cost or cost-effectiveness in coverage decisions (Neumann 2005). Consequently, Medicare and Medicaid cover all newly approved specialty drugs. Indeed, drugs to treat cancer accounted for a majority of Part B drug spending in 2004. While in theory private payers have more leeway to set coverage policies, *de facto* coverage (and reimbursement) policy for most specialty drugs follows that of Medicare's policies (Clemens and Gottlieb 2013).

Prior to 2006, Medicare reimbursed providers for purchasing and administering physician-administered specialty drugs as a percentage of the Average Wholesale Price ("AWP", a list price): 95% from 1998 to 2003 and 85% in 2004. Enacted as part of the 2003 Medicare Drug Improvement and Modernization Act (MMA), Medicare instituted a new average sales price (ASP) payment system intended to more closely reflect actual acquisition prices than AWP but with two notable exclusions: Medicaid best prices and rebates, and 340B discounts. Effective January 2006, Medicare changed reimbursements for Part B drugs to the manufacturers' national ASP two quarters prior plus a 6% markup (Jacobson, Alpert, Duarte 2012). The 2011 Budget Control Act reduced Medicare Part B reimbursement effective April 1, 2013, from ASP+6% to ASP+4.3%, where it remains currently. Recent industry reports suggest commercial insurance reimbursement may be more generous than ASP+4.3% (PBMI 2014).

These MMA policies were responses to the widely recognized fact that reimbursement for many physician-administered specialty drugs covered under outpatient medical insurance benefits had been well

in excess of their acquisition prices. Indeed, hospitals, many provider groups and specialty pharmacy outlets profit from the gap between drugs' acquisition price and reimbursement by insurers and patients, often termed the "spread" (U.S. GAO 2004; Barr, Towle, Jordan 2008; Barr, Towle 2011, 2012; Towle, Barr 2009, 2010; Towle, Barr, Senese 2012). According to the GAO, prior to 2006 many drugs were available for purchase by provider groups at acquisition prices averaging 13-34% below their AWP, while others – particularly generics -- were acquired at even significantly lower prices, largely due to PBM and GPO pricing negotiations. Due to statutory provisions, the spread can be substantial among drugs purchased under 340B discounts and Medicaid rebates for eligible patients.

By setting the ratio of drug reimbursement to ASP+6% through 2012 and ASP+4.3% thereafter, the MMA reform generated the largest reimbursement decline for physician-administered drugs in Medicare's history. For oncology drugs, the policy change represented a marked decline from the weighted average reimbursement-to-cost ratio of 1.22 in 2004, and an even larger decline relative to the years prior to the passage of the MMA when the AWP rather than ASP was used as the benchmark to measure costs (U.S. GAO 2004). Jacobson et al. 2010 plot payment rates for drugs commonly used to treat lung and other solid tumor cancers; they observe the payment change due to the MMA to be very dramatic for some drugs. However, the changes were heterogeneous, with some drugs facing no change and others even a slight increase.

Nevertheless, a 2006 survey of oncologists suggests those practicing in selected outpatient settings obtained 70 to 77% of their practice revenues from drug payments (Akscin, Barr, Towle 2007). Later surveys using 2009-11 data report over 50% of outpatient oncology practice revenues continued to be derived from the spread between drug acquisition costs, insurer reimbursements and patient payments (Towle, Barr 2009, 2010; Towle, Barr, Senese 2012). Due to these payment incentives, many outpatient specialty physicians, notably oncologists, report that they face financial incentives to administer chemotherapeutics with high "spread" (Malin et al. 2013). In addition, various studies suggest oncologists' drug choices are responsive to profit margins. Conti et al. (2012) found that the use of irinotecan decreased following patient expiration even though the price dropped by more than 80%, possibly reflecting declines in the spread between the reimbursement level and oncologists' acquisition cost. Jacobson et al. (2006, 2010, 2012) report that oncologists switched away from drugs that lost the most margin after MMA reform implementation and towards expensive drugs favored by the equalized 6% mark-up across all drugs.

SECTION 3: THE MODEL

In this section, we outline our empirical models of ANDA entrants as well as pricing and utilization effects among specialty drugs following LOE, grounding them in theoretical considerations.

3.1 Theoretical considerations and empirical findings for entry models. Classic economic theory has much to say about entrants' short-run decisions to invest in their capability to produce an undifferentiated product, in the context of their cost, demand and marginal revenue curves (Pindyck, Rubinfeld 2013). Notably, when the supply of production inputs is constrained and/or there are substantial fixed costs of entry, entry may be more limited than assumed in classical models (Tirole 1988; Mankiw, Whinston 1986; Bresnahan, Reiss 1988, 1991; Berry 1992). Berry and Reiss (2007) describe reduced form and structural models where for any given product market, the number of entrantss is a function of their fixed entry costs that may differ among entrants based on their scale and scope, and potential revenues related to the demand elasticity for this product relative to available substitutes and other production opportunities.

In the pharmaceutical market context, a number of empirical studies have relied on this intuition to study entry after a drug's LOE. Reiffen and Ward (2005) examined generic entry using data on 31 drugs experiencing LOE in the late 1980s and early 1990s. They find that more generic entrants enter and enter more quickly into markets when expected profits are greater. Scott-Morton (2000) conducted a market level analysis of 81 drugs undergoing LOE between 1986 and 1992, and found that drugs that have higher pre-patent expiration revenues and that are used to treat highly prevalent chronic diseases experience greater generic entry. Scott-Morton (1999) examined entrant characteristics associated with generic entry decisions. Among drugs undergoing patent expiration between 1984 and 1994, she finds a generic entrant's previous experience with a given type of drug formulation and therapeutic class increases the probability of similar subsequent generic entry. This work and others (Kyle 2006; Grabowski, Vernon 1992, 1996) suggest drug manufacturing economies of scope may be an important determinant of entry decisions. Outside the U.S., Iizuka (2009) examines the relative importance of drug reimbursement policies on the number of generic entrants in Japan between 2004 and 2006. She finds fewer generic entrants when the drug is subject to administrative pricing policies (drugs commonly used in the hospital) compared to those that are not (drugs commonly dispensed in the outpatient setting).

Based on this literature, we implement descriptive reduced form count models to examine molecule-specific, industry- and entrant-level determinants in the specialty drug market. The base model we estimate is of the following general form:

$$(1)\ \text{Mancount}(\text{entrants}_k)=F(Z_k\delta + X_i\beta)$$

where Mancount is the number of entrants having an approved ANDA for a given molecule, Z_k is a matrix of characteristics of drug market k that affect market size, while X_i is a matrix of entrants or molecule characteristics that predict the fixed cost of entry for entrant i into market k. Holding all else

equal, we expect to observe more entrants wanting to enter a market as potential market size increases and less entrants into drug markets where the manufacturing technology needed for production is highly specialized and entails large fixed costs. We assume regulatory cost differences among molecules are small and that we can control adequately for different manufacturing techniques for different product groups (Wiggins, Maness 2004; Caves et al. 1991; Grabowski, Vernon 1992, 1996). Year and year squared enter the model to help control for changes in regulatory and other fixed cost differences.

As discussed in the Background section, the 2003 MMA altered reimbursement and benefit policy between 2004 and 2006 for many drugs in our sample, and therefore may have affected specialty market entry patterns (Iizuka 2009). Specifically, provisions of the MMA: (1) lowered Medicare reimbursement for Part B drugs from 95% of AWP to 85% of AWP effective January 2004 ("MMA1"), (2) provided Medicare coverage to pharmacy dispensed, largely orally formulated drugs in January 2006 (Medicare Part D) ("MMA2"), and (3) instituted the new ASP+6% payment scheme in January 2006 ("MMA2"). To mark these events, we define two 0-1 indicator variables MMA1 and MMA2 that take on the value of one after January 2004 and January 2006, respectively. We also create interaction variables MMA1*Part B and MMA2*Part B defined as the product of the MMA indicator variables and whether the molform was covered by Part B. We include these dummies in our entrant count models.

Furthermore, while the MMA1 and MMA2 policies targeted all drugs covered under Part B, the impact of these changes varied across drugs depending on the magnitude of the payment changes. Following Jacobson et al. (2010, 2012), for each drug j, we compute the absolute value of the percentage change in reimbursement just before vs. after the MMA1 reform, and call the variable "MMA1bite":

$$MMA1bite = \Delta Payment_{j,04-05} = Abs\left|Log\left(Payment_{j,05}\right) - Log\left(Payment_{j,04}\right)\right|$$

where $Payment_{j,05}$ is the Medicare payment in quarter 1 of 2005 (based on ASP) for drug j and $Payment_{j,04}$ is the Medicare payment in quarter 4 of 2004 (95% of AWP); this variable takes on identical non-zero values in 2005Q1 and thereafter, and is zero before 2005Q1. We focus on this one-quarter change for the first reform because it is plausibly exogenous to manufacturer supply decisions.

However, as noted earlier, we do not use these measures to derive welfare implications of entry under existing and alternative policy regimes (similar to that pursued by Berry (1992) and Berry and Reiss (2007)) given the host of agency, information and moral hazard issues plaguing health care markets. Rather, as described in further detail below, we indirectly examine the welfare implications of LOE among these drugs by examining whether the neoclassical relationships among presumed price declines upon LOE and generic entry and volume increases hold.

3.2 Theoretical considerations -- price and use models. A number of empirical studies have relied on the framework proposed by Bresnahan and Reiss (1991) among others (Caves et al. 1991;

Grabowski, Vernon 1992, 1996; Frank, Salkever 1997; Wiggins, Maness 2004) to examine the relationship between product prices and the number of manufacturers. This framework posits a Cournot quantity setting model or an entry threshold model (Bresnahan, Reiss 1991), predicting prices should initially fall quickly and then steadily, gradually approaching marginal cost as additional entry occurs. Bresnahan and Reiss (1991) examined prices for dentists, auto repair shops and the like in geographically isolated county seats. They found prices decline significantly when the supplier count moves from two to three entrants, with an even larger price impact observed moving from three to four entrants, but smaller price impacts from subsequent entry; thus they conclude that frequently it requires only three or four entrants to approximate competitive conditions in these markets. They also find a significant difference between price estimates in concentrated county seats and unconcentrated urban markets, suggesting local product market conditions are important in determining price declines. Similarly, Wiggins and Maness (2004) find continuing price declines among drugs undergoing LOE as the number of manufacturers becomes large (more than five competitors). Reiffen and Ward (2005) find that generic drug prices fall with increasing number of competitors, but remain above long-run marginal costs until there are eight or more competitors. They also find the size and time paths of generic revenues and the number of entrants is greatly affected by expected market size.

Several other authors have reported very small changes in price associated with entry into drug markets after LOE and even price increases in some drug markets (Caves et al. 1991; Grabowski, Vernon 1992, 1996). Frank and Salkever (1992) developed a theoretical model to explain the anomaly of rising branded prices in the face of generic competition. Their model posits a segmented market where two consumer segments exist – a quality conscious brand loyal segment that continues to buy the established branded drug after generic entry and a price-conscious segment that is less brand loyal. Frank and Salkever (1997) report that branded prices rise and generic prices fall in response to LOE and generic entry. Ellison et al. (1997) and Griliches and Cockburn (1994) also find that average branded anti-infective prices rise with generic entry; Ellison et al. (1997) and Aitken et al. (2013) report similar findings. Notably, in all these studies, oral (not infused or injected) formulations constitute the vast majority of post-LOE entrants.

We draw on this literature to establish the plausibility of the presumed price drop following LOE among generic specialty drugs. Specifically, we first examine the relationship between supplier prices received by entrants (inflation-adjusted monthly total sales revenues/total standard unit use) and the number and nature (branded vs. generic) of entrants supplying the market (Caves et al. 1991; Grabowski, Vernon 1992, 1996; Frank, Salkever 1997; Wiggins, Maness 2004; Reiffen, Ward 2005). We then examine the extent to which supplier prices of the generic drug across entrants fall with generic entry, using the following Cournot model:

$$(2)\ P^*(n) = (a + cN) /(N+1)$$

in which we assume a roughly linear relationship between price and the inverse of the number of sellers. Like others, here we assume that at any given point in time the number of approved manufacturers, N, is exogenously determined reflecting FDA approval and decision timing uncertainty, as well as documented variability over time in the number of ANDA backlogs (Ellison et al. 1997; Scott-Morton 1999; 2000; Wiggens, Maness 2004).[2]

We then estimate reduced form models of utilization after generic entry as the "dual" of the Cournot model of price competition in Equation 2 (Grabowski, Vernon 1992, 1996; Berndt et al. 2003; Knittel, Huckfeldt 2012) using generalized least squares.[3] We estimate random effects regression models that quantify the importance of drug-specific demand and cost differences in influencing the use-supplier relationship (Wiggins, Maness 2004) having the following form:

$$(3)\ \ln Y_{kt} = \alpha + \beta_t + \kappa Z_k + \theta Post_{kt} + \varepsilon_{kt}$$

where Y_{kt} is the utilization volume of drug k at month t, α is a constant, β_t are time fixed effects capturing general changes in specialty drug demand, and κZ_k are effects from the characteristics of the molecule. The variable $Post_{kt}$ is an indicator variable denoting generic entry month-year for each molecule experiencing post-LOE generic entry in the sample. Positive estimates of θ suggest volume increases post-LOE (presumably reflecting increased quantity demanded from lower average molecule price post-LOE), whereas negative estimates suggest utilization declines post-LOE.

To interpret the hypothesized possible result (finding that $\theta<0$ in Equation (3)) we include in one specification whether LOE has an independent and negative effect on usage among physician-administered drugs after LOE, all else equal. In addition, LOE should act to induce institutional consumers to shift their demand away from low-cost generic specialty drugs towards high-priced branded alternatives when the drug is covered under insurers' outpatient medical benefit (where the absolute value of insurer reimbursement would be greater, holding all else constant) (Jacobson et al. 2010, 2012; Conti et al. 2012). We identify these independent effects on use by including in the model the variables that capture Medicare coverage in Part B and the MMA reimbursement and coverage changes outlined above.

[2] We must make this assumption for another reason. Only ANDA holders who were awarded "Paragraph IV" status in 2004 and thereafter are publicly listed by the FDA. See: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm047676.htm. ANDA holders who were unsuccessful in their Paragraph IV certifications are not publicly available; nor is the timing of the Paragraph IV application process, irrespective of award status.

[3] Duggan and Scott-Morton (2010) and Berndt and Aitken (2011) have found significant volume increases related to policy changes that act to decrease drug prices to consumers.

SECTION 4. DATA AND DESCRIPTIVE TRENDS

We obtained national monthly data on the use volume and retail and non-retail dollar sales of all specialty drugs by distributor from IMS Health Incorporated's National Sales Perspectives™ (NSP) database between January 2001 and December 2007. NSP data have been used in numerous published studies of pharmaceutical revenues and volumes. NSP data derive from a projected audit describing 100% of the national unit volume and dollar sales in every major class of trade and distribution channel for U.S. prescription pharmaceuticals. The NSP sample is based on over 1.5 billion annual transactions from over 100 pharmaceutical manufacturers and more than 700 distribution centers. NSP provides information on the molecule-specific chemical and branded names, route of administration, strength and the name of labeller. Each labeller-molecule-formulation ("molform") is uniquely identified in the dataset using the drug's NDC code; molform is the basic unit of analysis for all the main models. We also were able to uniquely identify labeller-molecule-formulation-strength using the drug's 11-digit NDC. This measure, "molform strength", is used in sensitivity analyses.

"Dollar sales" measures the amount of funds retail pharmacies, mail pharmacies, non-federal hospitals, federal facilities, long-term care facilities, clinics, home healthcare facilities, and miscellaneous facilities spent on a drug acquired from entrants and drug wholesalers. The prices reflected in this sales measure are the actual invoice prices outlets (e.g., pharmacies, hospitals, clinics) pay for the products, whether purchased directly from an entrant or indirectly via a wholesaler or chain warehouse. Invoice line item discounts are included, but prompt-payment discounts and bottom-line invoice discounts are not included. Rebates, typically paid by the manufacturer directly to a customer, insurer, or PBM, are not reflected in these data. Dollar sales are converted into 2012 U.S. dollars using the Consumer Price Index all urban inflation calculator. "Extended units" measures the number of single items (such as vials, syringes, bottles, or packet of tablets/capsules) contained in a unit or shipping package purchased by providers and pharmacies, but may include varying available doses and strengths.

Our NSP data covers the following ten World Health Organization's four-digit cancer-related anatomic therapeutic classes (ATCs): anti-emetics and anti-nauseants (A04A), alkylating agents (L01A), antimetabolites (L01B), vinca alkaloids (L01C), antineoplastic antibiotics (L02D), all other antineoplastics (L01X), cytostatic hormones (L02A), cytostatic hormone antagonists (L04B), other immune-suppressants (L04X), and detox ag a-neoplastic treatments (V03D). This sample frame has the advantage of including branded and generic versions of the same molecule having similar manufacturing requirements and including drugs that are covered under both insurers' pharmacy and medical benefits. ATC four-digit and more disaggregated ATC class designations are retained and coded for use in the sensitivity analyses.

The distribution of NDCs by ATC class is listed below in Table 1. The majority of drugs in the full sample fall into several categories: drugs used to treat "cancer" (antimetabolites, antineoplastics agents, other anti-neoplastic treatments – 215 of 752 in 2001, 312/1044 in 2007), "supportive" therapy (anti-emetics and anti-nauseants, cytostatic hormones, cytostatic hormone antagonists—332/752 in 2001,

Table 1. Count of unique sample NDCs by therapeutic class.

	Count of unique NDCs by Anatomic Therapeutic Class Designation						
ATC	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
A04A ANTIEMETCS+ANTINAUSEANTS	247	240	258	273	259	289	328
L01A ALKYLATING AGENTS	68	70	72	78	80	72	81
L01B ANTIMETABOLITES	117	114	114	120	125	128	130
L01C VINCA ALKALOIDS	55	59	66	67	75	73	67
L01D ANTINEOPLAS. ANTIBIOTICS	82	87	83	82	80	90	115
L01X ALL OTH. ANTINEOPLASTICS	40	42	53	91	107	121	133
L02A CYTOSTATIC HORMONES	63	64	67	73	74	75	74
L02B CYTO HORMONE ANTAGONISTS	22	29	49	52	54	55	55
L04X OTHER IMMUNOSUPPRESSANTS	0	0	0	0	0	12	12
V03D DETOX AG A-NEOPLAST TRMT	58	56	46	46	51	51	49
Grand Total	752	761	808	882	905	966	1044

457/1044 in 2007) and "other" (other immune-suppressants, antineoplastic antibiotics – 82/752 in 2001, 127/1044 in 2007).

According to economic theory, pre-LOE differences in fixed costs affect the subsequent number of generic entrants. Therefore, similar to Scott-Morton (1999; 2000), Iizuka (2009) and Wiggins and Maness (2004), we code formulations into several categories according to the type of specialized equipment needed to manufacture a drug and the cleanliness standards required in the manufacturing facility (oral solid tablets or capsules; injectable or infusible products; topical preparations; and other formulations, including ocular drugs, patches, and aerosols).

For each molecule, the earliest ANDA approval for each molform was identified using the FDA's comprehensive online listing Drugs@FDA. This method stratified the full sample (166 molforms) into three groups: (1) 41 molforms (25% of full sample) experiencing initial generic entry between January 2001 and July 2007, (2) 50 molforms (30%) experiencing generic entry prior to January 2001; and (3) 75 molforms (45%) only available as exclusively marketed "brands" between January 2001 and December 2007 (Appendix Table 1). Because of our focus on the extent and impact of generic entry, we excluded molforms in the (3) category from our analyses (all molforms are listed in Appendix Table 2), and instead focus primarily on category (1).

Among the 41 molforms experiencing generic entry in our study period, the majority underwent LOE in 2002 and 2004 (Appendix Table 2). 9 (22%) underwent generic entry on or following January 2006. 61% (25 out of 41 molforms) had FDA approved labels that indicated their use in combination therapy to treat cancer. Among this sample, we observed the following drug formulation pattern: 37%

oral and 63% infused/injected or otherwise physician-administered. Our check of Part B Medicare reimbursement schedules revealed 76% (31 of our 41 molforms experiencing initial LOE between 2001 and 2007) were covered by the Medicare Part B benefit (the remainder presumably covered under Part D benefits) (CMS 2014).

Using the FDA's comprehensive online listing we identified whether for a given molecule generic entry timing differed by formulation and/or strength. The subsequent entry of differing formulations (and/or strengths) among existing ANDAs may reflect a different underlying demand structure than with novel entrants, with the more commonly utilized formulations/strengths being produced earliest and/or certain formulations protected from entry by secondary patents. We found that the majority of molecules undergoing generic entry shared identical entry dates across multiple formulations; yet, a limited number of molforms experienced sequential entry by different strengths. Consequently, in our empirical models we estimate parameters first at the molform level and in sensitivity analyses at the molform-strength level.

The number of "entrants" for each molform and molform-strength was identified using the NSP and cross-checked using the FDA's Orange Book. Because litigation, regulatory labeling approval, and manufacturing startup issues can delay *de facto* entry beyond the *de jure* FDA approval date, we take the first month in which the NSP data indicate positive volume and sales dollars as the initial ANDA entry date. We count the number of such entrants at twelve months after the initial ANDA entry to allow for delayed entry due to 180-day exclusivity provisions involving Paragraph IV challenges., To flag and delete repackagers to avoid double counting supply we used the RedBook and checked all entrant names for repackaging using a websearch.

We identified 63 entrants distributing at least one cancer drug undergoing initial generic entry in our study period. In Appendix Table 3, we enumerate these entrants and the total number of molforms produced by them among all drugs in the parent sample. As expected from our institutional review, we find production of these drugs concentrates in several entrants. Branded manufacturers of drugs undergoing LOE in our sample are primarily limited to the following: Abbott, AstraZeneca, Bayer Healthcare, Bristol-Myers Oncology, Genzyme, GSK, Novartis, Pfizer, Roche and Watson. Among generic entrants, APP, Bedford Laboratories, Teva Parenteral ME and Teva Pharmaceuticals dominate the production of drugs undergoing initial LOE in our sample. We also observe growth in these ANDA entrants' commitment to the production of all generic cancer drugs over time, as the number produced is generally larger in 2007 than in earlier years, although year-to-year changes are occasionally negative (Table 2). We use these branded/generic entrant designations for examining pricing trends at the molform-entrant level after LOE.

Table 2. Number of all sample cancer drugs produced by top ANDA manufacturers.

Number of cancer drugs produced by top manufacturers of drugs undergoing LOE				
	APP	BEDFORD LABS	TEVA PARENTERAL ME	TEVA PHARMACEUTICA
2001		16		9
2002		15		9
2003	12	16		12
2004	16	20	20	14
2005	17	21	19	15
2006	16	23	22	18
2007	20	26	22	19

We construct measures of pre-patent expiration brand *revenues* and *ln revenues*, adopting a definition of "market" size consisting of sales only by the branded molecule in the four complete quarters prior to LOE (average monthly revenue: 439 thousand (standard deviation 452 thousand, min 0, max 1722); average ln revenue: 5.6 (standard deviation 6.2, min 0, max 13.2)) (Frank and Salkever 1997; Scott-Morton 1999; Iizuka 2009). Following Scott-Morton (1999), we also constructed a measure of the *difference in revenue* defined as the value of the difference between the revenue potential from the entry opportunity relative to that of the entrants' existing mean generic NDC portfolio from all drugs enumerated in the NSP (monthly average =381.6 thousand, standard deviation=538 thousand, min=-816, max=1599). To the extent the entrants' existing portfolios consist of old vintages of off-patent drugs having declining sales and the entry being considered is that for a widely utilized newer molecule having large sales volume, we expect this difference measure will positively affect probability of current entry. We transform by using the difference log form of this measure (monthly mean=5.9, standard deviation=1.5, min=-2.5, max=7.4) in the estimated model and its square.

While previous literature has focused on using pre-LOE revenues (and its square, both typically log-transformed) as measures of potential market size post-LOE, we augment these by constructing a measure reflecting the number of distinct conditions treated by the medicines. Specifically, we construct a measure of indication count, inclusive of FDA on-label approved and off-label Medicare reimbursed, measured in the year prior to LOE that is likely correlated with potential future revenues.[4] The number of indications for which an NDC was reimbursed for use in the U.S. population in each year (average 6, standard deviation 9) is taken from the MICROMEDEX DRUGDEX Evaluations database, one of several compendia approved by Congress to guide CMS reimbursement policy (Conti et al. 2012). This identified FDA approved (on-label) and off-label indications that were contemporaneously reimbursed by the Centers for Medicare and Medicaid Services.

[4] Incentives for entrants to seek additional indications for reimbursements diminish considerably after LOE, although the off-patent brand may pursue a "branded generic" strategy in which it markets a combination product consisting of the off-patent brand and a generic drug.

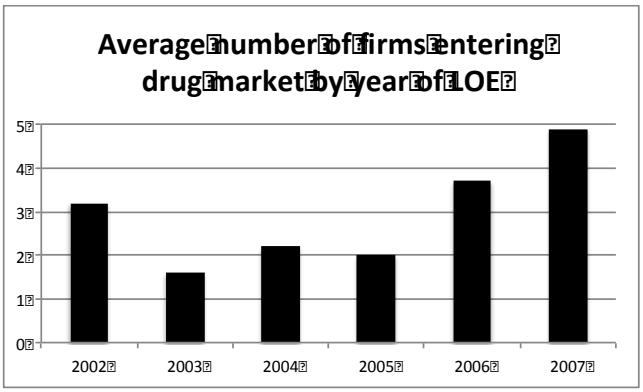
Finally, we matched all sample molforms and molform-strengths with the UUDIS to determine dates of any shortages including resolved shortages, if present.[5] No sample molforms and molform-strengths were reported in short supply between January 2001 and December 2007. Interestingly, by 2008 or thereafter 18/41 (44%) of our drug sample were reported in short supply, with 67% of these (12/18) having experienced initial LOE prior to 2005. The majority of these eventually shorted molforms (14 out of 18) were parentally formulated.

SECTION 5. RESULTS

A. Count models for descriptive purposes

Bearing in mind the caveats on entrant counts created by the presence of considerable contract manufacturing activities, we first describe the average number of generic entrants per molform experiencing LOE by year of LOE (Table 3). We observe the average number to range between 1.66 and 4.9 manufacturers over all years, and what appears to be an upwards trend in entry count in 2006 and 2007 compared to previous years, from a low of 1.66 in 2003 to a high of 4.9 in 2007.

Table 3. Average number of ANDA manufacturers entering a new molform after LOE, by year of LOE.



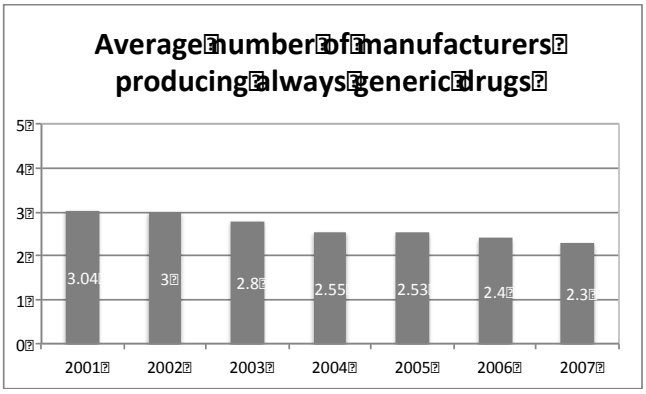
Furthermore, average entrant counts differ by drug formulation: over all years, oral drugs exhibit an average of 6.26 (standard deviation: 2.7, max: 11) manufacturers entering after LOE, while physician-administered drugs exhibit an average of 4.5 (standard deviation: 2.7, max: 9) manufacturers entering after LOE.

To place these observations into wider industry level context, we also calculated the average number of manufacturers of always generic cancer drugs available throughout the study period (Appendix

[5] http://www.ashp.org/drugshortages/current/;
http://www.ashp.org/menu/DrugShortages/ResolvedShortages.

Table 2; Table 4). We observe the average number of manufacturers producing these drugs to be declining gradually but steadily from 3.04 in 2001 to 2.3 in 2007.

Table 4. Average number of manufacturers producing always generic molforms.



Interestingly, the patterns of entry and exit among specialty cancer drugs undergoing LOE during our study periods appear quite diverse, as is illustrated in the various panels of Table 5. For example, the first column (Example 1) in Table 5 documents a situation in which the pioneer branded manufacturer (Pierre Fabre Pharma, bolded) continues to market vinorelbine IAC in injectable and intravenous formulations following LOE in 2003 and throughout the remaining study period. We also observe injectable and intravenous formulation ANDA entry in vinorelbine IAC by Baxter Pharma Division and Sicor Pharma in 2003, Bedford Labs and Teva Parenteral ME in 2004 and APP and Hospira in 2005. We observe Sicor Pharma exiting this drug market in 2004 and Baxter Pharm Division exiting in 2007. Merger and acquisition activity likely explains the apparent exit by Sicor Pharma and entry by Teva Parenteral ME in 2004 (Table 6) – Teva acquired Sicor in 2004, and likely subsequently consolidated the two generic products into one market offering.

In other cases, the pioneer brand is observed to exit the molform market after initial LOE, as is seen in Example 2 of Table 5. Here, the supplier of the branded version of carboplatin IAC injectable and regular intravenous (Bristol-Myers Oncology, bolded) faced LOE in 2004 and remained in the market only through 2005. In 2004, we observe APP, Baxter Pharma Division, Bedford Labs, Cura Pharm, Hospira, Teva Parenteral ME and Watson Labs and in 2005 OTN Pharmaceutical entering this molform market. The final column of Table 5 documents a somewhat similar pattern of exit by the pioneer brand manufacturer (AstraZeneca, bolded) for the oral anticancer drug tamoxifen, albeit in

Table 5. Observed patterns of entry and exit after LOE among selected sample molforms.

Table 5. Observed patterns of entry and exit after LOE

	Example 1: Innovator stays in the market after LOE	Example 2: Innovator exits the market after LOE	
Year	VINORELBINE TARTRATE,INJECT,IV	CARBOPLATIN TARTRATE,INJECT,IV,REG	TAMOXIFEN CITRATE,ORAL,SOL,TAB/CAP,RE
2001	PIERRE FABRE PHARM	BRISTOL-MYERS ONCO	ASTRAZENECA
2002	PIERRE FABRE PHARM	BRISTOL-MYERS ONCO	ASTRAZENECA BARR LABS
2003	BAXTER PHARM DIV PIERRE FABRE PHARM SICOR PHARM	BRISTOL-MYERS ONCO	ASTRAZENECA BARR LABS MYLAN ROXANE TEVA PHARMACEUTICA
2004	BAXTER PHARM DIV BEDFORD LABS PIERRE FABRE PHARM TEVA PARENTERAL ME	APP BAXTER PHARM DIV BEDFORD LABS BRISTOL-MYERS ONCO HOSPIRA TEVA PARENTERAL ME WATSON LABS	ASTRAZENECA BARR LABS MYLAN ROXANE TEVA PHARMACEUTICA WATSON LABS
2005	APP BAXTER PHARM DIV BEDFORD LABS HOSPIRA PIERRE FABRE PHARM TEVA PARENTERAL ME	APP BAXTER PHARM DIV BEDFORD LABS BRISTOL-MYERS ONCO CURA PHARM HOSPIRA TEVA PARENTERAL ME WATSON LABS	ASTRAZENECA MYLAN RANBAXY PHARM ROXANE TEVA PHARMACEUTICA WATSON LABS
2006	APP BAXTER PHARM DIV BEDFORD LABS HOSPIRA PIERRE FABRE PHARM TEVA PARENTERAL ME	APP BAXTER PHARM DIV BEDFORD LABS CURA PHARM HOSPIRA TEVA PARENTERAL ME WATSON LABS	ASTRAZENECA MYLAN ROXANE TEVA PHARMACEUTICA WATSON LABS
2007	APP BEDFORD LABS HOSPIRA PIERRE FABRE PHARM TEVA PARENTERAL ME	APP BAXTER PHARM DIV BEDFORD LABS CURA PHARM GENERAMEDIX HOSPIRA TEVA PARENTERAL ME WATSON LABS	MYLAN ROXANE TEVA PHARMACEUTICA WATSON LABS

2007 several years after LOE in 2002, and staggered ANDA entry by Barr Labs, Mylan, Roxane, Teva Pharmaceutica and Watson Labs in 2004. Here too, the observed Barr Labs exit from this molform in 2005 might be related to the formalization of its acquisition by Teva several years later (see Table 6).

These observations suggest mergers and acquisitions among generic entrants (horizontal consolidation) and branded entrants (vertical consolidation) occurring between 2000 and 2009 could alter our results of entrant count. To check, we identified mergers and acquisitions among manufacturers using the *SDC Platinum*, a collection of databases on companies registered in the U.S. and a product of Thomson Reuters Financial Securities Data available through the University of Chicago's electronic library. This categorization was double-checked using a web search of all manufacturers and the trade press. The presence, date and type of consolidation is reported in Table 6.

Table 6: Consolidation activity among manufacturers in our sample.

	Merging firm	Acquiring firm	Completion year
1	GREENSTONE LTD	PFIZER	2003
2	ABBOTT PHARM PRODS	HOSPIRA	2004
3	SICOR PHARM	TEVA PHARMACEUTICA	2004
4	mayne pharmaceuticals	HOSPIRA	2007
5	abraxis pharm	APP	2007
6*	king	JHP PHARM	2007
7	BARR LABS	TEVA PHARMACEUTICA	2008
8	APP	fresenius	2008
9	wyeth ayerst	PFIZER	2009
10	medimmune oncology	ASTRAZENECA	2013

* jhp was formed out of assets from King and other companies

CAPITALIZED manufacturer names indicate manufacturers producing drugs undergoing LOE in our sample

To analyze factors contributing to the diverse entry patterns, we estimated random effects generalized least squares count models with ln mancount (log number of manufacturers) as the dependent variable for each molform based on the 2001-2007 pooled cross-section and time series data; in sensitivity analyses, we re-estimate using molform-strength as the unit of observation. Since with a Poisson model there was over-dispersion (estimated variance greater than mean), estimates presented in Table 7 are based on the negative binomial model. Consistent with the raw averages, we observe less entry into injectable formulations after LOE (all Models). There is also greater entry into the cancer therapeutic class, and less entry into other classes after LOE (all Models). Another robust finding across Models is that ln preentry revenue positively impacts number of manufacturers. Consistent with this finding we also observe in each of the estimated models, the greater the number of ln indications for which the molform is recommended, the greater the number of manufacturers of that molform (Models 1-5). However, ln preentry revenue squared flips in sign across Models. Models 3-5 report another modestly robust finding that when ln revenues of the candidate molform is much greater than the mean revenue per product of the incumbent portfolio of molform products (a positive ln revenue difference), the number of manufacturers for a molform increases, although the negative estimated coefficient on the squared ln revenue difference variable indicates this positive impact declines as the ln revenue difference increases. This suggests that all else equal, entrants may face a tradeoff as they contemplate additional generic entry between incremental revenue gained and the greater fixed and/or sunk production costs incurred. Finally, note that while in Models 4-5 the positive estimated coefficient on the month post-MMA1 indicator variable and the negative estimate on the post-MMA1*part B covered interaction variable have the expected signs suggesting MMA reimbursement policy changes affected entry, these estimates are not statistically significant.

Table 7. Manufacturer Count Model Negative Binomial Regression Results.

	Model 1, ln mancount			Model 2, ln mancount			Model 3, ln mancount			Model 4, ln mancount			Model 5, ln mancount		
	coeff	std error	p>|t|	coeff	std error	p>|t|	coeff	std error	p>|t|	coeff	std error	p>|t|	coeff	std error	p>|t|
injectable	-0.27	0.17	0.133	-0.59	0.24	0.04	-0.51	0.25	0.05	-0.92	0.21	0.001	-0.95	0.31	0.001
ln indications	0.9	0.42	0.001	0.9	0.1	0.001	0.9	0.1	0.001	0.9	0.11	0.001	1.03	0.12	0.001
cancer therapeutic class	1.2	0.2	0.001	0.65	0.28	0.02	0.8	0.3	0.007	0.66	0.25	0.008	0.48	0.28	0.07
other therapeutic class	-0.62	0.33	0.064	-0.34	0.5	0.355	-0.35	0.53	0.355	-0.73	0.44	0.03	-0.84	0.44	0.03
time (months starting with January 2001)	0.004	0.0009	0.001	0.006	0.0007	0.001	0.006	0.0007	0.001	0.002	0.0004	0.001	0.002	0.0004	0.001
time squared (months starting with January 2001)	0.002	0.00001	0.001	0.001	0.00001	0.001	0.0001	0.00001	0.001	-0.00003	0.000007	0.001	-0.00003	0.000007	0.001
ln revenue pre LOE ($USD2012)	0.007	0.003	0.001	0.009	0.0003	0.001	0.01	0.0004	0.001	0.002	0.0003	0.001	0.002	0.0003	0.001
ln revenue pre LOE squared ($USD2012)	0.000004	0.0000002	0.001	0.000003	0.0000002	0.001	0.000003	0.0000002	0.001	-0.000003	0.0000002	0.001	-0.000003	0.0000002	0.001
ln revenue pre LOE diff ($USD2012)				-0.05	0.01	0.001	0.05	0.01	0.001	0.02	0.007	0.038	0.02	0.007	0.038
ln revenue pre LOE diff squared ($USD2012)				-0.02	0.002	0.001	-0.02	0.002	0.001	-0.005	0.001	0.001	-0.005	0.001	0.001
mma1 (2004)							0.12	0.07	0.09	0.004	0.04	0.93	0.01	0.05	0.83
mma1 * part b covered							-0.06	0.07	0.43	-0.03	0.05	0.6	-0.02	0.05	0.7
mma2 (2006)										0.03	0.06	0.61	0.04	0.06	0.54
mma2 * part b covered										0.95	0.06	0.001	0.96	0.06	0.001
mma1 bite													-0.28	0.03	0.001
_constant	1.9	0.19	0.001	1.73	0.24	0.001	1.94	0.26	0.001	0.44	0.22	0.04	1.31	0.24	0.001
adjusted R-squared (overall)	0.28			0.49			0.5			0.84			0.84		
n=	3444			3444			3444			3444			3444		

B. Supplier Prices following LOE

As an initial analysis of the impact of LOE on supplier prices, we examine average monthly inflation adjusted prices, separately for oral and injectable/infusible molforms, before LOE and generic entry, and after LOE and generic entry, aggregated over brand and generic versions for each molform. As is seen in Table 8, for both oral and infused/injected specialty drugs, average monthly prices are lower post-LOE and generic entry than pre-LOE. Interestingly, aggregate price declines appear to be larger among physician-administered infused/injected drugs (34%) than among orally formulated drugs (21% decline).

Table 8. Raw inflation adjusted prices and ln prices before and after LOE.

Table 8. Raw inflation adjusted prices before and after LOE.

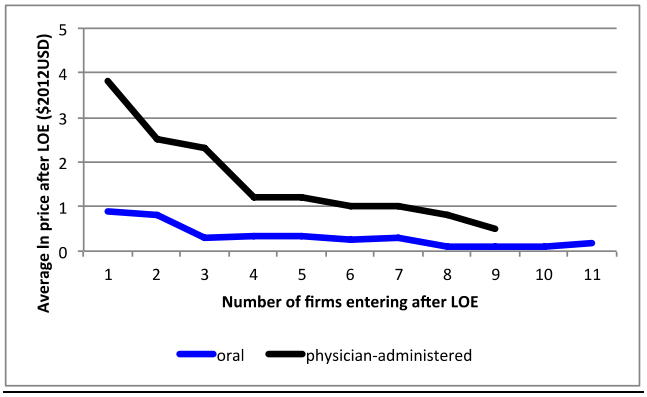
	Before LOE		After LOE		After-Before		
	Monthly ave.	Stand. Error	Monthly ave.	Stand. Error	Difference	Stand. Error	% change
oral (n=15)							
prices ($2012USD)	1.26	0.04	1	0.01	**-0.26**	0.04	**-21%**
physician-administered infused/injected (n=26)							
prices ($2012USD)	135.6	2.7	90	3.5	**-45.6**	7	**-34%**

Bolded = statistically significant at p-value<.01 level.

Next, to examine the relationship between supplier prices following LOE and the number of manufacturers, we first plotted average monthly ln prices ($2012US) observed in the last quarter of 2007 against the total number of unique entrants in all years following LOE (including the pioneer brand, if it is still on the market), stratified by oral vs. infused/injected or otherwise physician-administered formulation. Results are displayed in Table 9, with ln supplier prices on the vertical axis and total number of unique manufacturers following LOE on the horizontal axis. Two sets of results are striking. First, the level of ln prices for oral formulations is much lower than that for infused/injected or otherwise physician-administered drugs, up until there are about nine unique manufacturers of the formulation. Second, for infused/injected or otherwise physician-administered drugs, when the number of manufacturers increases from one to two, average ln prices fall about 25-30%, there is another even larger proportional drop in ln price as the number of manufacturers increases from three to four, but in the range between four and seven manufacturers, ln prices of these drugs are relatively stable, and after that as

additional manufacturers of infused/injected or otherwise physician-administered drugs enter, the average ln price continues to fall. This suggests that for infused/injected or otherwise physician-administered cancer drugs, unlike the case for oral solids, price declines accelerate as the number of manufacturers increases.

Table 9. Relationship between Ln inflation adjusted estimated supplier prices ($USD 2012) and manufacturer count after LOE.



A more rigorous method for analyzing the relationship between supplier prices following LOE and the total number of manufacturers (but bearing in mind potential measurement error in supplier counts from unobserved and time-varying outsourcing to contract manufacturing organizations) is via regression analysis. Results of estimating a regression equation via ordinary least squares with ln (inflation adjusted) supply price as the dependent variable are presented separately in Table 10 for generic and branded formulations following LOE, and for oral and infused/injected or otherwise physician-administered formulations.

Table 10. Relationship between inflation adjusted supplier price ($2012USD) and manufacturer counts, by formulation and LOE status.

	Oral molforms			Injected and infused or otherwise physician-administered formulated molforms		
	coefficient	*se*	*p-value*	*coefficient*	*se*	*p-value*
generic, underwent LOE						
lnmancount	-0.77	0.03	0.0001	-0.22	0.017	-12.54
lnmancount squared	-0.01	0.005	0.051	0.02	0.004	0.0001
year	0.26	0.05	0.0001	-0.29	0.03	0.0001
n=	287			1678		
adjusted r-square=	0.16			0.12		
branded, underwent LOE						
lnmancount	0.07	0.02	0.002	0.49	0.04	0.0001
lnmancount squared	0.07	0.005	0.0001	-0.04	0.006	0.0001
year	-0.52	0.04	0.0001	0.26	0.04	0.0001
n=	161			1318		
adjusted r-square=	0.12			0.05		

We begin with the oral molforms. As seen in the top left panel, following LOE generic prices fall sharply as ln mancount (which now includes only ANDA holders, not the brand) increases, and this

decline accelerates ever so slightly as the square of ln mancount increases. Holding ln mancount and its square constant, prices increase annually (year =1 in 2001, year=2 in 2002, etc.). For the off-patent but branded oral molforms following LOE (bottom left panel), the relationship of supplier prices with ln mancount is very different. Specifically, ln (inflation adjusted) supplier prices of branded oral molforms increase with growth in ln mancount, and this price increase accelerates with the square of ln mancount, suggesting that for oral brands, the ability to differentiate themselves from generics post-LOE enables them to continue commanding premium prices. However, this ability to increase price declines with time, other things equal, as the estimated coefficient on the year variable is negative, large and significant.

By contrast, as seen in the top right corner of Table 10, for injected and infused molforms following LOE, ln (inflation adjusted) supplier prices fall much less steeply as ln mancount increases than do oral molforms, and this price decline decelerates as the square of ln mancount increases; however, ln (inflation adjusted) supplier prices fall as time increases. The situation is very different for branded injected and infused molforms following LOE (bottom right panel): prices of these branded non-oral formulations increase with ln mancount, but at a decreasing rate (the estimate on the squared ln mancount variable is negative and significant). In summary, for both oral and injected/infused molforms, following LOE prices of generic molforms fall as ln mancount increases (with the price decline being much steeper for oral than injected/infused formulations), but for branded molforms following LOE, prices increase as ln mancount grows, with the price increase being steeper for injected/infused than oral formulations. These results suggest post-LOE price competition among manufacturers is less intense for injected/infused than oral formulations.

C. Impact of LOE on Utilization Volume

While measures of utilization volume are relatively straightforward for oral formulations (number tablets or capsules – what IMS Health calls *standard units*, or total milligrams of active pharmaceutical ingredient), for infused, injected or otherwise physician-administered formulations, the measure of utilization volume is more ambiguous. IMS Health defines *extended units* as the number of tablets, capsules, milliliters, ounces, etc. of a product shipped in each unit. This number is calculated by multiplying the number of units by the product size. Another volume measure is an "each", which represents "the number of single items (such as vials, syringes, bottles, or packet of pills) contained in a unit or shipping package and purchased by providers and pharmacies in a specific time period. An each is not a single pill or dosage of medicine (unless one package consists of a single dose), but may be the same as a unit if the unit does not subdivide into packages. Eaches are usually used to examine usage of

injectable products. Eaches are most meaningful at the package level, since packages and their subunits may contain different quantities of strengths and volumes."[6]

As an initial analysis of the impact of LOE on utilization volume, in Table 11 we examine three measures of volume – average monthly extended units, average monthly eaches and average monthly inflated adjusted sales ($US 2012) separately for oral and injectable/infusible molforms, before LOE and generic entry, and after LOE and generic entry, again aggregated over brand and generic versions for each molform. As seen in Table 11, regardless of which volume measure used, average aggregate brand plus generic monthly utilization is greater post-LOE and generic entry than pre-LOE and generic entry for both oral and physician-administered infused/injected drugs.

Table 11. Raw Use and Inflation Adjusted Sales Trends Before and After LOE by formulation.

Table 11. Raw Use and Inflation Adjusted Sales Trends Before and After LOE by formulation.

		Before LOE		After LOE		After-Before		
		Monthly Ave.	Stand. Error	Monthly Ave.	Stand. Error	Difference	Stand. Error	% Change
oral (n=15)								
	extended units	1508.4	18.4	2759	24.7	1250.3	30.8	82.9%
	eaches	121.5	1.7	158.5	1.6	37.03	2.29	30.5%
	sales ($2012USD)	1356.1	27.8	1985.5	30.3	629.42	41.1	46.4%
physician-administered infused/injected (n=26)								
	extended units	438.75	14.2	656.2	12.6	217.5	19.01	49.6%
	eaches	27.8	11.04	47.96	0.44	20.16	11.05	72.5%
	sales ($2012USD)	1596.4	20.9	2506.6	23.4	910.2	31.4	57.0%

Bolded = statistically significant at p-value<.01 level.

However, a closer examination focused on the share of molforms within each aggregate category experiencing an increase reveals that these aggregate trends mask heterogeneity across drugs within oral and within infused/injectable formulations, and across these formulations. First, using the extended units measure of volume, 40% of the molforms experienced a statistically significant utilization increase, while 47% experienced a statistically significant utilization decrease; for the infused/injected formulations, these percentages were 27% and 42%, respectively. We therefore explored a more detailed analysis of the impact of LOE on utilization volume involving estimation of various generalized least squares models with random effects in which the dependent variable is the log of volume, where volume is measured in extended units. Here again, the unit of observation is the molform-month. In the specification of Model 1 in Table 12, the omitted reference case for the various indicator variables is pre-LOE time periods, an oral formulation, and a supportive therapeutic (e.g., an anti-nausea drug to mitigate side effects). We find that the estimated coefficient on the generic entry year indicator variable (taking on the value of one post-LOE and initial generic entry, else zero among oral formulated drugs) is positive and significant. Also

[6] From email correspondence between Berndt and Terry McMonagle at the IMS Institute for Healthcare Informatics, September 4, 2013.

consistent with the findings in Table 11, although the estimated coefficient on the main effect injectable variable is negative (for the pre-LOE time periods), here we find that aggregate average monthly volume increases are large for injectable/infusible drugs following LOE, i.e. the parameter estimate on the injectable-entry year interaction variable is positive and significant. While estimates on the therapeutic class indicator variables are statistically insignificant, coefficients on the continuous time variable (1 in January 2001, 2 in February 2001, etc.) and its square are small in magnitude, and negative and positive, respectively.

In Model 2, the various MMA indicator variables and interactions with Part B variables are added to Model 1. The omitted reference case for these variables is pre-MMA time periods for an oral drug covered by Medicare Part D. While estimates on the oral post LOE (entry year dummy) and physician-administered post LOE (entry year dummy*injectable interaction) variables in Model 2 are robust in sign to their Model 1 counterparts, in Model 2 the magnitude of the use change is about twice that reported in Model 1. In Model 2 the estimates on MMA1 and MMA2 are both positive and significant, implying utilization of oral molforms experiencing LOE increased after these policy changes. However, we find estimates on the MMA-Part B interaction variables (interpreted as differences from the omitted pre-MMA-Part D variables) are both negative and significant, suggesting that the volume increases are concentrated among drugs covered under Part D, not Part B, and that post-MMA1 it is the part B injectables whose volume decreases. Note that the absolute value of the estimated parameter on the post-MMA1*part B interaction value is larger than that of the post-MMA1 main effect variable, although this is not the case for the MMA2 interaction and main effect variable parameter estimates. Hence it appears the reimbursement reduction for physician-administered Part B variables that took effect in MMA1 (between 2004Q4 and 2005Q1) is associated with a substantial decline in volume utilization.

Finally, in Model 3, we added an additional variable "MMA1bite" to quantify the magnitude of (the absolute value of the) negative reimbursement shocks for some Part B covered drugs but not others in 2004. Interestingly, except for the injectable and Part B main effects variables, estimated coefficients and their statistical significance for variables included in Model 3 are remarkably robust to their values in Models 2. Molecules which experienced very large drops in reimbursement between 2004 and 2005 are found to have very large and statistically significant volume declines, holding all else constant.

Table 12. Estimated volume changes using GLS random effects.

Table volume model results, random effects

	Model 1, ln extended units			Model 2, ln extended units			Model 3, ln extended units		
	coeff	std error	p>|t|	coeff	std error	p>|t|	coeff	std error	p>|t|
entry year dummy	0.24	0.02	0.001	0.51	0.02	0.001	0.51	0.024	0.228
injectable	-2.2	0.87	0.01	-2.12	0.94	0.02	-0.72	1.14	0.527
entry year dummy * injectable	0.39	0.03	0.001	0.63	0.03	0.001	0.63	0.03	0.001
ln indications	-0.1	0.42	0.813	-0.1	0.39	0.78	-0.08	0.37	0.83
cancer therapeutic class	-0.12	0.96	0.89	-0.1	0.87	0.9	-0.13	0.84	0.88
other therapeutic class	1.3	1.6	0.4	1.33	1.4	0.355	1.36	1.38	0.33
time (months starting with January 2001)	-0.004	0.001	0.001	-0.0007	0.001	0.43	-0.0007	0.001	0.43
time squared (months starting with January 2001)	0.00008	0.00001	0.001	0.00003	0.00001	0.01	0.00003	0.00001	0.01
part b covered				0.59	1.02	0.56	1.26	1.03	0.22
mma1 (2004)				0.49	0.03	0.001	0.49	0.03	0.001
mma2 (2006)				0.26	0.03	0.001	0.26	0.03	0.001
mma1 * part b covered				-1.3	0.03	0.001	-1.3	0.03	0.001
mma2 * part b covered				-0.14	0.03	0.001	-0.14	0.03	0.001
mma1 bite							-2.4	1.15	0.04
_constant	5.01	0.86	0.001	4.5	0.92	0.001	4.75	0.9	0.001
Adjusted R squared (overall)	0.1			0.16			0.26		
sigma_u	2.02			2.17			2.09		
sigma_e	0.76			0.79			0.8		
rho	0.87			0.88			0.88		
number of groups	41			41			41		
n=	3444			3444			3444		

5.5 Sensitivity Analyses

To assess the robustness of our principal findings to alternative specifications and metrics, we undertook a number of investigations. For example, we examined use of revenue variables measured as the mean over varying molforms in the twenty-four and six months preceding ANDA entry (rather than 12 months); time-varying indication counts for each molform; orphan/priority review designation as a distinct measure of clinical quality; and the presence or absence of available therapeutic substitutes as determined by the FDA. We also pursued the construction and use of several market-specific measures of supplier level costs, including parent and subsidiary relationships among manufacturers based on Table 6, and FDA regulatory cost compliance measures. We estimated count models for entry in the first year, and two years following patent expiration. Finally, we re-estimated all price and use models using molform-strength as the unit of analysis. Our main findings are robust to each of these alternative definitions and/or specifications. They are available upon request from the lead author.

Finally, we recognize our measure of generic entry may violate our assumption of "simultaneous information" for a number of reasons. This includes the fact that the timing of generic entry may be endogenous to the number of manufacturers entering into the market due to Paragraph IV filings and notifications (Panattoni 2011), although our count assessed at 12 months after initial generic entry should largely eliminate any effects from possible endogeneity, particularly given the widely documented increase in the number of backlogged ANDA filings remaining unresolved at the FDA. We plan to examine this issue in future research.

SECTION 6: DISCUSSION AND POLICY IMPLICATIONS

This research has reported a number of findings regarding entry and pricing following LOE for specialty drugs that differ from patterns reported for non-specialty oral solid tablets and capsules. First, as expected from our institutional review highlighting relatively large fixed costs and economies of scale and scope for injectable/infusible drug manufacturing, we find pre-LOE production of cancer drugs to concentrate in several manufacturers, including Abbott, AstraZeneca, Bayer Healthcare, Bristol-Myers Oncology, Genzyme, GSK, Novartis, Pfizer, Roche and Watson. Among generic manufacturers, APP, Bedford Laboratories, Teva Parenteral ME and Teva Pharmaceuticals dominate the production of drugs undergoing initial LOE in our sample. We also observe the number of entrants into specialty drug LOEs to range between 1.66 and 4.99 manufacturers over all years, and what appears to be an upwards trend in entry count in 2006 and 2007 compared to previous years. The limited number of manufacturers we observe entering the production of specialty drugs post-LOE is considerably smaller in magnitude that that reported in previous studies of entry into non-specialty drugs. Nevertheless, these findings are consistent with that of U.S. Department of Health And Human Services, ASPE (2011), documenting that manufacturers of generic cancer drugs experienced a general increase in the quantity and mix of drugs they were producing in 2006 and thereafter, compared to 2000. A close inspection of entry trends into selected molforms also reveals several intriguing patterns. For example, among several specialty molecules, we observe exit by the branded supplier after LOE, as well as delayed and sequential ANDA entry into a given molecule undergoing LOE.

We also find evidence to suggest both entry and exit to be occurring among generic cancer drugs. For example, the average number of manufacturers of always generic cancer drugs available throughout the study period declines from 3.04 in 2001 to 2.3 in 2007. This winnowing of overall supplier counts per generic drug is consistent with other reports suggesting that merger and acquisition activities, outsourcing and/or discontinuations of previously offered generic drugs were common business practices during this period (U.S. Department Of Health And Human Services, ASPE 2011; FDA 2011). These results suggest generic manufacturers of cancer drugs may have been exiting from producing very old generic drugs and instead entering into segments experiencing initial LOE that offered potentially more profitable opportunities.

Economic theory suggests that the number of average entrants per new LOE is likely related to molecule specific rationales and wider industry trends. We find evidence to support this theory; in each model presented the importance of molecule formulation and pre-LOE revenues appear to affect supplier counts. These former results are similar to those reported by Scott-Morton (1999; 2000) and Iizuka (2009) and are likely related to the insurer coverage and reimbursement incentives operative in this specific drug market. The latter results are similar to those reported by Scott-Morton (1999; 2000), Wiggins and Maness (2004) and Reiffen and Ward (2005) who also show that among their drug samples, pre-LOE

sales measures explain a significant proportion of variation in the number of sellers in the post-LOE study period.

Finally, we do not find evidence to suggest the presence of tighter administered pricing policies for drugs clearly targeted by 2003 Medicare Modernization Act reforms (MMA1 in 2004) negatively affected the number of manufacturers of generic drugs as they became available. In fact, among new opportunities we document robust and increasing entry after MMA1 implementation. This finding is tempered when we expressly examine the impact of negative price reimbursement declines due to MMA reforms implemented in 2004 on entry patterns.

We also find that physician-administered drugs have higher inflation-adjusted supplier prices compared to orally formulated drugs both before and after LOE. Furthermore, as expected, across all drug formulations we find inflation-adjusted supplier prices are negatively and statistically significantly related to the number of generic entrants producing them following LOE. Although the magnitudes of these price- supplier effects are considerably larger here for physician-administered drugs, the qualitative effects reported also mimic those found for oral generic and branded drugs following LOE (e.g., Aitken et al. 2013). Additional average price reductions continue to increase among drugs offered by five or more manufacturers (and the sign of the estimated parameter on the number of manufacturers squared is negative), particularly among physician-administered drug formulations and contrary to the literature examining non-specialty drugs. This result is intriguing, since Gaynor and Vogt (2003), Mankiw and Whinston (2002), Berry and Reiss (2007), among others, suggest that anticipated profits in a variety of industries drops to zero after the entry of four or more manufacturers. Yet, we are well aware that another potential endogeneity issue arises here reflecting unobserved or partially observed differences between drugs that might affect both their prices and price changes and the number of manufacturers (Reiffen, Ward 2005). Following Reiffen and Ward (2005), we believe this endogenity produces an upward effect on the price changes we estimate among our sample following LOE. Thus, our price estimates should be considered an upper bound on the effect of entrants following LOE on price competition. A close examination of the endogeneity of entry and how it may impact prices in the specialty drug market is an important future research topic.

We also find evidence to suggest branded prices rise and generic prices fall in response to LOE and generic entry. This result is consistent with Frank and Salkever (1997), Ellison et al. (1997), Griliches and Cockburn (1994) and Aitken et al. (2013). We believe we are the first to report this finding in a specialty drug sample.

Our efforts provide contemporary estimates of volume utilization following the generic entry of specialty drugs. In all models, volume appears to increase substantially following generic entry, consistent with the usual assumptions regarding the negative relationship between prices and quantity

demanded and empirical work among non-specialty drugs undergoing LOE. However, these usage trends are much less robust among physician-administered formulations. Rather, the results of these models suggest MMA reimbursement reforms may have shifted utilization away from injectable Part B reimbursed generic drugs after LOE, all else equal. This finding is also consistent with that reported by Jacobson et al. (2006, 2010, 2012) and Conti et al. (2012).

Regarding the welfare implications of these utilization results in this market, we acknowledge that they are complicated given the general aging of the population and increasing detection of cancer in combination with technological change supporting increased demand for combination products, all else equal (Scherer FM 1993; Cutler, Huckman, Kolstad 2010). It is also unclear how to interpret these findings given the extent of simultaneous misuse, underuse, and overuse among cancer drugs (Conti et al. 2012) and the complicated agency relationship which rewards physicians and hospitals for the use of branded, highly reimbursed cancer drugs in treating cancer in the outpatient setting (Jacobson et al. 2006, 2010, 2012, 2013; Conti et al. 2012). As we discussed in the background section, even this relationship among oral, pharmacy benefit covered specialty drugs is complicated by the lack of institutional incentives in hospitals such as the tiered formularies adopted by payers to increase consumer price sensitivity regarding the use of generic drugs (Grabowski, Vernon 1992, 1996; Aitken et al. 2009). Lastly, finding mixed effects on utilization pattern, Caves et al. (1991), Berndt et al. (2003) and Knittel and Huckfeldt (2012) suggest simultaneous declines in advertising and product reformulation introductions may act to mitigate the relationship between presumptive price declines and utilization increases associated with drugs following LOE. One advantage of our sample choice is that these changes have limited applicability to interpreting potential volume shifts among specialty drugs, since neither advertising nor new product formulations have been widely documented among physician-administered specialty drugs (Kornfield et al. 2013). Whether this trend is consistent across oral and injected/infused drugs among many other specialty therapeutic classes is an important direction for future research.

Nevertheless, we believe we can derive "second-best" welfare consequences from our price and utilization results. Recall there is a substantial literature examining the welfare effects of a monopolist implementing third degree price discrimination relative to requiring a uniform monopoly price. We argue here that this literature may be important in understanding plausible welfare implications of our findings. Notably, among others, Varian (1989, pp. 619-623) has shown that in the context of two groups of consumers and under quite general conditions, a necessary condition for welfare to increase under price discrimination relative to uniform pricing is that total volume increases under price discrimination. In the current context, readers can consider uniform pricing as that occurring when the product has patent protection, i.e., the brand price prior to LOE. Following LOE, however, there are two groups of customers – the cost-conscious consumers who are attracted by low generic prices, and the consumers

who are more brand loyal; these two groups of customers pay different prices for the same bioequivalent product (Frank, Salkever 1997). Our pricing results suggest that supplier-prices of generic drugs decline quite substantially after generic entry, while supplier-prices of branded drugs rise after LOE; this finding is consistent with Frank and Salkever's work. Taken together, we suggest that our finding that post-LOE aggregate volumes of the molecule (brand plus generics) are greater than pre-LOE brand volumes supports a necessary condition for economic welfare gains among consumers of at least orally formulated specialty drugs to be satisfied, holding the above concerns in mind.

We conclude with several policy implications of our study. First, we note the number of manufacturers marketing specialty injectable/infusible drugs post-LOE in 2001-2007 is considerably smaller than has been observed for oral tablet and capsule formulations in previous studies. We have argued that one likely reason for this more limited supply post-LOE is that manufacturing specialty injectable/infusible formulations likely involves greater fixed and variable costs than for oral solid capsules and tablets. In this context, it is worth noting that provisions of the 2012 Generic Drug User Fee Amendments (GDUFA) not only assess one-time user fees for manufacturers of ANDAs, but also entail annual payments by manufacturers to the FDA that vary by whether the manufacturing site is domestic or foreign, and whether the manufactured product is the active pharmaceutical ingredient or the final dosage form ("fill and finish"). This increase in manufacturing fixed costs can be expected to incentivize brand and generic drug manufacturers to outsource their manufacturing to contract manufacturing organizations (CMOs), and since the annual user fee is site rather than product-specific, it creates additional economies of scope that generate incentives for CMOs to increase the number of products manufactured at their site. To the extent that in addition CMOs are able to produce the same molform for different ANDA holders, the increased fixed costs and scale economies brought about by GDUFA may result in the further outsourcing of manufacturing to CMOs and thereby reduce the number of distinct organizations manufacturing injectable/infusible drugs post-LOE. How these increased fixed costs in the presence of both increased economies of scope and scale will affect supplier prices is unclear, but worthy of further analysis.

Second, many of the injectable specialty drugs in our sample of 41 molecules experiencing initial LOE in 2001-7 are similar to currently patent protected injectable biologics in the U.S. (Grabowski et al. 2011). Thus, the patterns of entry, price and use after LOE among specialty drugs we document may provide some insight into what might occur as patents of U.S. biologics expire and they experience initial biosimilar entry. Yet we caution our reader: each of the drugs in our sample -- branded and generic versions of specialty drugs -- has been designated "fully interchangeable" by the FDA. Biosimilar entrants will likely be therapeutic substitutes to the branded pioneer but not necessarily "fully interchangeable" drugs. Second, the generic injectable/infused drugs in our 2001-2007 sample are mostly

traditional APIs dissolved in water; the manufacturing complexity and costs of biologics soon going experiencing initial LOE in the U.S. are likely much greater than in our 2001-2007 sample. For both these reasons, our estimates likely provide only an upper bound to the entry and a lower bound on the price effects likely to occur as biologics go off patent in the U.S.

Third, on drug shortages, 44% of our sample undergoing LOE between 2002 and July 2007 (18 molforms) were reported in short supply in 2008 or thereafter, 67% of these molforms (12 molforms) underwent generic entry prior to 2005, and the majority of these eventually shorted molforms (14 out of 18) were parentally formulated. A thorough examination of the importance of the limited number of manufacturers of generic drugs previous to shortage reports and the potential correlations among the MMA, utilization trends and entry patterns is an important avenue for future empirical work. We note in passing that Stromberg (2014) reports strikingly similar temporal patterns of shortages among oral drugs, suggesting that time-varying factors common to injectable and oral drugs may be one of the root causes of shortages. Stromberg reports a statistically significant relationship between FDA regulatory activity (inspections and citations) and drug shortage rates over time.

Fourth, our review of the specialty drug market raises questions about researchers', stakeholders' and policy makers' definition of drug "manufacturers" in that the increasingly important presence of time-varying and unobservable contract manufacturing practices complicates and may even undermine the definition of unique "manufacturers" entering this market, well beyond the usual concerns regarding ongoing merger and acquisition activities. Under current statute (and partly in response to recent observed drug shortages), NDA and ANDA labelers are obligated to notify FDA of plans to discontinue drug manufacturing as well as any changes in manufacturing responsibilities, including the outsourcing of drug production after initial approval. How well labelers comply with this requirement, and how accessible the resulting data are to the FDA, is an important issue meriting further scrutiny.

Furthermore, FDA sources say that it is common for a drug labeler to qualify a new facility to manufacture its drug due to either the loss of the old facility or to changing market demand prompting the manufacturer to acquire additional capacity. In these cases, NDA and ANDA labellers often turn to contract manufacturers. However, data on the use of CMOs and their identity upon initial filings and subsequent changes is not publicly accessible through the web portal Drugs@FDA and is exempt from being released under the Freedom of Information Act (the FDA generally treats non-public business relationships as confidential commercial or financial information, exempting it from public disclosure). A proprietary data source, Truven's RedBook, maintains more updated information on which NDA and/or ANDA NDC labellers are actively offering a drug in the U.S. market, but even this source does not identify contract manufacturing arrangements. The identity and nature of base ingredient manufacturing (APIs) for many drugs, also collected by FDA from ANDA manufacturers, are similarly shielded from

public scrutiny.

We believe these increasingly important business practices have at least two implications for measuring the extent of generic competition. First, these arrangements make it challenging for regulators charged with monitoring competition in the generic and branded drug market to predict reliably what the concentration of specialty drug supply of drugs will be following mergers, acquisitions and/or closures of NDA or ANDA manufacturers and/or contract manufacturing facilities supplying drugs to the U.S. market. These relationships can make economic models of such activity and their potential competitive effects on supply and/or prices by agencies such as the Department of Justice or Federal Trade Commissions inaccurate, particularly if overlapping supply is present before merger and acquisition activity between the two parties. Second, under these arrangements the public and their guardians are unable to quickly identify sources and root causes of supply disruptions when supply or quality lapses occur. How best to formulate market level solutions to supply lapses given extreme informational asymmetry regarding which manufacturers are actually producing these drugs or their base ingredients is a very challenging and perplexing issue.

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APPENDIX TABLES

Molecules/forms in sample		
Generic always	Generic entry	Entry year
n=50	n=41	
BLEOMYCIN INJECT,MULT ADM REG	ARSENIC IV INJECT,IV REG	2006
CARMUSTINE IV INJECT,IV REG	BUSULFAN ORAL,SOL,TAB/CAP RE	2003
CHLORAMBUCIL ORAL,SOL,TAB/CAP RE	CARBOPLATIN IV INJECT,IV REG	2004
CISPLATIN IV INJECT,IV REG	CLADRIBINE INJECT,MULT ADM REG	2004
CLADRIBINE IV INJECT,IV REG	CLADRIBINE IV INJECT,IV REG	2004
CYTARABINE INJECT,MULT ADM REG	CYCLOPHOSPHAMIDE IV INJECT,IV REG	2004
DACARBAZINE IV INJECT,IV REG	CYCLOPHOSPHAMIDE ORAL,SOL,TAB/CAP	2004
DAUNORUBICIN IV INJECT,IV REG	DEXRAZOXANE IV INJECT,INFUSION REG	2005
DOLASETRON IV INJECT,IV REG	DEXRAZOXANE IV INJECT,IV REG	2005
DOXORUBICIN IV INJECT,IV REG	DIMENHYDRINATE INJECT,MULT ADM REG	2004
ESTRAMUSTINE ORAL,SOL,TAB/CAP RE	DIMENHYDRINATE ORAL,SOL,CHEWABLE	2002
ETOPOSIDE IV INJECT,IV REG	DIMENHYDRINATE ORAL,SOL,TAB/CAP RE	2002
ETOPOSIDE ORAL,SOL,TAB/CAP RE	DIMENHYDRINATE!SCOPOLAMINE ORAL,SO	2002
FLOXURIDINE IV INJECT,IV REG	EPIRUBICIN IV INJECT,IV REG	2006
FLUOROURACIL DDC DERM,CREAM	FLUDARABINE IV INJECT,IV REG	2003
FLUOROURACIL DDL DERM,LIQUID/LOTION	IDARUBICIN IV INJECT,IV REG	2004
FLUOROURACIL IV INJECT,IV REG	IFOSFAMIDE IV INJECT,IV REG	2004
FLUOROURACIL TOZ OTHER TOPICALS	IFOSFAMIDE!MESNA SAZ OTHER SYSTEMICS	2004
FLUTAMIDE ORAL,SOL,TAB/CAP RE	LEUPROLIDE IAA INJECT,IM REG	2004
FRUCTOSE!GLUCOSE!PHOSPHORIC ACID DLL DR	LEUPROLIDE IAE INJECT,SUBCUT REG	2004
FRUCTOSE!GLUCOSE!PHOSPHORIC ACID DSC DR	LEUPROLIDE IAF INJECT,SUBCUT L.A	2004
GOSERELIN IAF INJECT,SUBCUT L.A	LEUPROLIDE SAZ OTHER SYSTEMICS	2004
HYDROXYUREA ORAL,SOL,TAB/CAP RE	LEUPROLIDE!LIDOCAINE SAZ OTHER SYSTEMIC	2004
LEUCOVORIN IAG INJECT,MULT ADM REG	MERCAPTOPURINE ORAL,SOL,TAB/CAP RE	2004
LEUCOVORIN ORAL,SOL,TAB/CAP RE	MITOXANTRONE IAC INJECT,IV REG	2006
LOMUSTINE ORAL,SOL,TAB/CAP RE	ONDANSETRON IAC INJECT,IV REG	2006
MECHLORETHAMINE IAC INJECT,IV REG	ONDANSETRON IVR INJECT,IV PIGBACK	2007
MECLIZINE DSC ORALS,SOL,CHEWABLE	ONDANSETRON OLL ORALS,LIQ,NON-SPEC L	2007
MECLIZINE ORAL ORALS,SOL,TAB/CAP RE	ONDANSETRON OLR ORALS,LIQ,READY-MDE	2007
MEGESTROL OLR ORALS,LIQ,READY-MDE	ONDANSETRON OSO ORALS,SOL,TAB/CAP DT	2007
MEGESTROL ORAL ORALS,SOL,TAB/CAP RE	ONDANSETRON ORAL ORALS,SOL,TAB/CAP RE	2007
MESNA IAC INJECT,IV REG	PENTOSTATIN IAC INJECT,IV REG	2007
MESNA ORAL ORALS,SOL,TAB/CAP RE	SCOPOLAMINE IWT INSRT/IMPLANT,TRANSD	2003
METHOTREXATE IAG INJECT,MULT ADM REG	SCOPOLAMINE ORAL ORALS,SOL,TAB/CAP RE	2003
METHOTREXATE ORAL ORALS,SOL,TAB/CAP RE	TAMOXIFEN ORAL ORALS,SOL,TAB/CAP RE	2002
METHOXSALEN IAX INJECT,OTHER REG	TAMOXIFEN OLL ORALS,LIQ,NON-SPEC L	2002
METHOXSALEN YAZ ALL OTHERS	TRETINOIN ORAL ORALS,SOL,TAB/CAP RE	2007
MITOMYCIN IAC INJECT,IV REG	TRIMETHOBENZAMIDE IAA INJECT,IM REG	2002
MITOTANE ORAL ORALS,SOL,TAB/CAP RE	TRIMETHOBENZAMIDE ORAL ORALS,SOL,TAB/CAP	2002
PACLITAXEL IAC INJECT,IV REG	TRIMETHOBENZAMIDE RRS RECTALS SYST,SUPP	2002
PEGASPARGASE IAG INJECT,MULT ADM REG	VINORELBINE IAC INJECT,IV REG	2003
PROCARBAZINE ORAL ORALS,SOL,TAB/CAP RE		
PROCHLORPERAZINE IAG INJECT,MULT ADM RE		
PROCHLORPERAZINE ORAL ORALS,SOL,TAB/CAP		
PROCHLORPERAZINE RRS RECTALS SYST,SUPPO		
STREPTOZOCIN IAC INJECT,IV REG		
TESTOLACTONE ORAL ORALS,SOL,TAB/CAP RE		
THIOTEPA IAC INJECT,IV REG		
VINBLASTINE IAC INJECT,IV REG		
VINCRISTINE IAC INJECT,IV REG		

Table Number of Packages associated with each molform

molform	molformlabel	molform*packages count mean	sd	min	max
	BLUE INDICATES EXPERIENCES GENERIC ENTRY IN STUDY PERIOD				
	All molform	1.3503012	0.60843	1	10
1	ALEMTUZUMAB IAC INJECT,IVREG	1	0		
2	ALITRETINOIN DDG DERM,GEL	1	0		
3	ALTRETAMINE DSR ORALS,SOL,TAB/CAP RE	1	0		
4	AMIFOSTINE IAC INJECT,IVREG	1	0		
5	ANASTROZOLE DSR ORALS,SOL,TAB/CAP RE	1	0		
6	APREPITANT DSR ORALS,SOL,TAB/CAP RE	1	0		
7	ARSENIC IAC INJECT,IVREG	1	0		
8	ASPARAGINASE IAG INJECT,MULT ADMREG	1	0		
9	AZACITIDINE IAE INJECT,SUBCUT REG	1	0		
10	BEVACIZUMAB IAC INJECT,IVREG	1	0		
11	BEXAROTENE DDG DERM,GEL	1	0		
12	BEXAROTENE DSR ORALS,SOL,TAB/CAP RE	1	0		
13	BICALUTAMIDE DSR ORALS,SOL,TAB/CAP RE	1	0		
14	BLEOMYCIN IAG INJECT,MULT ADMREG	4.7	2	1	7
15	BORTEZOMIB IAC INJECT,IVREG	1	0		
16	BUSULFAN IAC INJECT,IVREG	1	0		
17	BUSULFAN DSR ORALS,SOL,TAB/CAP RE	1	0		
18	CAPECITABINE DSR ORALS,SOL,TAB/CAP RE	1.125	0.33	1	2
19	CARBOPLATIN IAC INJECT,IVREG	4.3	2.81	1	10
20	CARMUSTINE IAC INJECT,IVREG	1	0		
21	CARMUSTINE IJS INSRT/IMPLANT,SUB-DE	1	0		
22	CETUXIMAB IAC INJECT,IVREG	1	0		
23	CHLORAMBUCIL DSR ORALS,SOL,TAB/CAP RE	1	0		
24	CISPLATIN IAC INJECT,IVREG	1.8	0.8	1	3
25	CLADRIBINE IAC INJECT,IVREG	1.5	0.5	1	2
26	CLADRIBINE IAG INJECT,MULT ADMREG	1	0		
27	CLOFARABINE IAC INJECT,IVREG	1	0		
28	CYCLIZINE DSR ORALS,SOL,TAB/CAP RE	1	0		
29	CYCLOPHOSPHAMIDE IAC INJECT,IVREG	1.7	0.8	1	3
30	CYCLOPHOSPHAMIDE DSR ORALS,SOL,TAB/CAP	1.7	0.7	1	3
31	CYTARABINE IAG INJECT,MULT ADMREG	1.5	0.5	1	2
32	CYTARABINE IAZ INJECT,OTHER LA	1	0		
33	DACARBAZINE IAC INJECT,IVREG	2.2	1	1	4
34	DACTINOMYCIN IAC INJECT,IVREG	1	0		
35	DASATINIB DSR ORALS,SOL,TAB/CAP RE	1	0		
36	DAUNORUBICIN IAC INJECT,IVREG	1.6	0.6	1	3
37	DECITABINE IAC INJECT,IVREG	1	0		
38	DENILEUKIN DIFTITOX IAK INJECT,INFUSION	1	0		
39	DEXRAZOXANE IAC INJECT,IVREG	1	0		
40	DEXRAZOXANE IAK INJECT,INFUSION REG	1	0		
41	DIMENHYDRINATE IAG INJECT,MULT ADMREG	1	0		
42	DIMENHYDRINATE DSC ORALS,SOL,CHEWABLE	1	0		
43	DIMENHYDRINATE DSR ORALS,SOL,TAB/CAP RE	3.7	2	1	8
44	DIMENHYDRINATE!SCOPOLAMINE DSR ORALS,SO	1	0		
45	DOCETAXEL IAC INJECT,IVREG	1	0		
46	DOLASETRON IAC INJECT,IVREG	1	0		
47	DOLASETRON DSR ORALS,SOL,TAB/CAP RE	1	0		
48	DOXORUBICIN IAC INJECT,IVREG	2.4	1	1	4
49	DRONABINOL DSR ORALS,SOL,TAB/CAP RE	1	0		
50	ELECTROLYTE REPLACERS DLL ORALS,LIQ,NON	1	0		
51	EPIRUBICIN IAC INJECT,IVREG	1.75	2	1	7
52	ERLOTINIB DSR ORALS,SOL,TAB/CAP RE	1	0		
53	ESTRAMUSTINE DSR ORALS,SOL,TAB/CAP RE	1	0		
54	ETOPOSIDE IAC INJECT,IVREG	2.2	1	1	4
55	ETOPOSIDE DSR ORALS,SOL,TAB/CAP RE	1.2	0.33	1	2
56	EXEMESTANE DSR ORALS,SOL,TAB/CAP RE	1	0		
57	FLOXURIDINE IAC INJECT,IVREG	3	0	3	3
58	FLUDARABINE IAC INJECT,IVREG	1.9	1	1	5
59	FLUOROURACIL DDC DERM,CREAM	1.2	0.42	1	2
60	FLUOROURACIL DLE DERM,LIQUID/LOTION	1.4	0.5	1	2
61	FLUOROURACIL IAC INJECT,IVREG	1.5	0.5	1	2
62	FLUOROURACIL TOZ OTHER TOPICALS	1	0		
63	FLUTAMIDE DSR ORALS,SOL,TAB/CAP RE	2	1	1	4
64	FOSAPREPITANT DSR ORALS,SOL,TAB/CAP RE	1	0		
65	FRUCTOSE!GLUCOSE!PHOSPHORIC ACID DLL DR	1	0		
66	FRUCTOSE!GLUCOSE!PHOSPHORIC ACID DSC DR	1	0		
67	FULVESTRANT IAA INJECT,IMREG	1	0		
68	GALLIUM IAK INJECT,INFUSION REG	1	0		
69	GEFITINIB DSR ORALS,SOL,TAB/CAP RE	1	0		
70	GEMCITABINE IAC INJECT,IVREG	1	0		
71	GEMTUZUMAB IDZ OGAMICIN IAC INJECT,IVREG	1	0		
72	GINGER DSZ ORALS,SOL,OTHER	1	0		
73	GOSERELIN IAF INJECT,SUBCUT LA	1	0		
74	GRANISETRON IAC INJECT,IVREG	1	0		
75	GRANISETRON DLL ORALS,LIQ,NON-SPEC L	1	0		
76	GRANISETRON DSR ORALS,SOL,TAB/CAP RE	1	0		
77	HISTRELIN SAZ OTHER SYSTEMICS	1	0		
78	HYDROXYUREA DSR ORALS,SOL,TAB/CAP RE	4.4	2.6	1	7
79	IBRITUMOMAB TIUXETAN SAZ OTHER SYSTEMIC	1	0		
80	IDARUBICIN IAC INJECT,IVREG	1.5	0.5	1	2
81	IFOSFAMIDE IAC INJECT,IVREG	2.3	1	1	4
82	IFOSFAMIDE!MESNA SAZ OTHER SYSTEMICS	1.5	0.5	1	2
83	IMATINIB DSR ORALS,SOL,TAB/CAP RE	1	0		
84	IRINOTECAN IAC INJECT,IVREG	1	0		
85	IXABEPILONE SAZ OTHER SYSTEMICS	1	0		
86	LAPATINIB DSR ORALS,SOL,TAB/CAP RE	1	0		
87	LENALIDOMIDE DSR ORALS,SOL,TAB/CAP RE	1	0		
88	LETROZOLE DSR ORALS,SOL,TAB/CAP RE	1	0		
89	LEUCOVORIN IAG INJECT,MULT ADMREG	2.34	1	1	4
90	LEUCOVORIN DSR ORALS,SOL,TAB/CAP RE	1.9	0.8	1	3
91	LEUPROLIDE IAA INJECT,IMREG	1.4	0.48	1	2
92	LEUPROLIDE IAE INJECT,SUBCUT REG	1	0		
93	LEUPROLIDE IAF INJECT,SUBCUT LA	1	0		
94	LEUPROLIDE SAZ OTHER SYSTEMICS	2	0.8	1	3
95	LEUPROLIDE!LIDOCAINE SAZ OTHER SYSTEMIC	1	0		
96	LOMUSTINE DSR ORALS,SOL,TAB/CAP RE	1	0		
97	MECHLORETHAMINE IAC INJECT,IVREG	1	0		
98	MECLIZINE DSC ORALS,SOL,CHEWABLE	2	1	1	3
99	MECLIZINE DSR ORALS,SOL,TAB/CAP RE	4	2	1	10
100	MEDROXYPROGESTERONE IAB INJECT,IM LA	1	0		
101	MEGESTROL DLR ORALS,LIQ,READY-MDE	2.3	1.5	1	5
102	MEGESTROL DSR ORALS,SOL,TAB/CAP RE	3.5	2.5	1	11
103	MELPHALAN IAC INJECT,IVREG	1	0		
104	MELPHALAN DSR ORALS,SOL,TAB/CAP RE	1	0		
105	MERCAPTOPURINE DSR ORALS,SOL,TAB/CAP RE	2	1	1	3
106	MESNA IAC INJECT,IVREG	3.5	1.8	1	6
107	MESNA DSR ORALS,SOL,TAB/CAP RE	1	0		
108	METHOTREXATE IAG INJECT,MULT ADMREG	1.8	0.8	1	3
109	METHOTREXATE DSR ORALS,SOL,TAB/CAP RE	3.3	2.7	1	9
110	METHOXSALEN IAX INJECT,OTHER REG	1	0		
111	METHOXSALEN YAZ ALL OTHERS	1	0		
112	MITOMYCIN IAC INJECT,IVREG	2.4	1	1	4
113	MITOTANE DSR ORALS,SOL,TAB/CAP RE	1	0		
114	MITOXANTRONE IAC INJECT,IVREG	2	2	1	6
115	NABILONE DSR ORALS,SOL,TAB/CAP RE	1	0		
116	NELARABINE IAC INJECT,IVREG	1	0		
117	NILOTINIB DSR ORALS,SOL,TAB/CAP RE	1	0		
118	NILUTAMIDE DSR ORALS,SOL,TAB/CAP RE	1	0		
119	ONDANSETRON IAC INJECT,IVREG	2.7	2.6	1	10
120	ONDANSETRON IVR INJECT,IVPIGBACK	1.6	1	1	4
121	ONDANSETRON DLL ORALS,LIQ,NON-SPEC L	1.5	0.5	1	2
122	ONDANSETRON DLR ORALS,LIQ,READY-MDE	1	0		
123	ONDANSETRON DSO ORALS,SOL,TAB/CAP DT	2.3	1.8	1	6
124	ONDANSETRON DSR ORALS,SOL,TAB/CAP RE	2.25	2.5	1	10
125	OXALIPLATIN IAC INJECT,IVREG	1	0		
126	PACLITAXEL IAC INJECT,IVREG	4.5	2.6	1	9
127	PALIFERMIN IAC INJECT,IVREG	1	0		
128	PALONOSETRON IAC INJECT,IVREG	1	0		
129	PANITUMUMAB IAK INJECT,INFUSION REG	1	0		
130	PEGASPARGASE IAG INJECT,MULT ADMREG	1	0		
131	PEGYLATED LIPOSOMAL DOXORUBICIN IAC INJ	1	0		
132	PEMETREXED IAC INJECT,IVREG	1	0		
133	PENTOSTATIN IAC INJECT,IVREG	1	0.4	1	2
134	PORFIMER IAC INJECT,IVREG	1	0		
135	PROCARBAZINE DSR ORALS,SOL,TAB/CAP RE	1	0		
136	PROCHLORPERAZINE IAG INJECT,MULT ADMRE	1.6	0.74	1	3
137	PROCHLORPERAZINE DSR ORALS,SOL,TAB/CAP	2.8	1.5	1	6
138	PROCHLORPERAZINE RRS RECTALS SYST,SUPPO	2.9	2	1	6
139	PROMETHAZINE RRS RECTALS SYST,SUPPOST	1	0		
140	RITUXIMAB IAK INJECT,INFUSION REG	1	0		
141	SCOPOLAMINE WTI NSRT/IMPLANT,TRANSD	1.4	0.5	1	2
142	SCOPOLAMINE DSR ORALS,SOL,TAB/CAP RE	1	0		
143	SORAFENIB DSR ORALS,SOL,TAB/CAP RE	1	0		
144	STREPTOZOCIN IAC INJECT,IVREG	1	0		
145	SUNITINIB DSR ORALS,SOL,TAB/CAP RE	1	0		
146	TAMOXIFEN DLL ORALS,LIQ,NON-SPEC L	1	0		
147	TAMOXIFEN DSR ORALS,SOL,TAB/CAP RE	2.8	1.7	1	6
148	TEMOZOLOMIDE DSR ORALS,SOL,TAB/CAP RE	1	0		
149	TEMSIROLIMUS SAZ OTHER SYSTEMICS	1	0		
150	TENIPOSIDE IAC INJECT,IVREG	1	0		
151	TESTOLACTONE DSR ORALS,SOL,TAB/CAP RE	1	0		
152	THIOTEPA IAC INJECT,IVREG	1.3	0.5	1	2
153	TOPOTECAN IAC INJECT,IVREG	1	0		
154	TOREMIFENE DSR ORALS,SOL,TAB/CAP RE	1	0		
155	TOSITUMOMAB SAZ OTHER SYSTEMICS	1.5	0.5	1	2
156	TRASTUZUMAB IAC INJECT,IVREG	1	0		
157	TRETINOIN DSR ORALS,SOL,TAB/CAP RE	1.1	0.4	1	2
158	TRIMETHOBENZAMIDE IAA INJECT,IMREG	1	0		
159	TRIMETHOBENZAMIDE DSR ORALS,SOL,TAB/CAP	1.4	0.5	1	2
160	TRIMETHOBENZAMIDE RRS RECTALS SYST,SUPP	1.3	0.5	1	2
161	TRIPTORELIN IAB INJECT,IM LA	1	0		
162	VALRUBICIN IAX INJECT,OTHER REG	1	0		
163	VINBLASTINE IAC INJECT,IVREG	1	0		
164	VINCRISTINE IAC INJECT,IVREG	1	0		
165	VINORELBINE IAC INJECT,IVREG	3.8	2.3	1	8
166	VORINOSTAT DSR ORALS,SOL,TAB/CAP RE	1	0		

molform	molformno	onlabel	offlabel	totalindications
ARSENIC IAC INJECT,IV REG	7	1	1	2
BUSULFAN OSR ORALS,SOL,TAB/CAP RE	16	3	2	5
CARBOPLATIN IAC INJECT,IV REG	19	2	17	19
CLADRIBINE IAG INJECT,MULT ADM REG	25	1	8	9
CLADRIBINE IAC INJECT,IV REG	26	1	8	9
CYCLOPHOSPHAMIDE IAC INJECT,IV REG	29	18	16	34
CYCLOPHOSPHAMIDE OSR ORALS,SOL,TAB/CAP	30	18	16	34
DEXRAZOXANE IAK INJECT,INFUSION REG	39	2	1	3
DEXRAZOXANE IAC INJECT,IV REG	40	2	1	3
DIMENHYDRINATE IAG INJECT,MULT ADM REG	41	1	1	2
DIMENHYDRINATE OSC ORALS,SOL,CHEWABLE	42	1	1	2
DIMENHYDRINATE OSR ORALS,SOL,TAB/CAP RE	43	1	1	2
DIMENHYDRINATE!SCOPOLAMINE OSR ORALS,SO	44	1	1	2
EPIRUBICIN IAC INJECT,IV REG	51	1	11	12
FLUDARABINE IAC INJECT,IV REG	58	1	8	9
IDARUBICIN IAC INJECT,IV REG	80	1	6	7
IFOSFAMIDE IAC INJECT,IV REG	81	1	24	25
IFOSFAMIDE!MESNA SAZ OTHER SYSTEMICS	82	1	24	25
LEUPROLIDE IAA INJECT,IM REG	91	4	7	11
LEUPROLIDE IAE INJECT,SUBCUT REG	92	4	7	11
LEUPROLIDE IAF INJECT,SUBCUT L.A	93	4	7	11
LEUPROLIDE SAZ OTHER SYSTEMICS	94	4	7	11
LEUPROLIDE!LIDOCAINE SAZ OTHER SYSTEMIC	95	4	7	11
MERCAPTOPURINE OSR ORALS,SOL,TAB/CAP RE	105	1	5	6
MITOXANTRONE IAC INJECT,IV REG	114	1	0	1
ONDANSETRON IAC INJECT,IV REG	119	4	1	5
ONDANSETRON IVR INJECT,IV PIGBACK	120	4	1	5
ONDANSETRON OLL ORALS,LIQ,NON-SPEC L	121	4	1	5
ONDANSETRON OLR ORALS,LIQ,READY-MDE	122	4	1	5
ONDANSETRON OSO ORALS,SOL,TAB/CAP OT	123	4	1	5
ONDANSETRON OSR ORALS,SOL,TAB/CAP RE	124	4	1	5
PENTOSTATIN IAC INJECT,IV REG	133	1	3	4
SCOPOLAMINE JWT INSRT/IMPLANT,TRANSD	141	2	1	3
SCOPOLAMINE OSR ORALS,SOL,TAB/CAP RE	142	2	1	3
TAMOXIFEN OSR ORALS,SOL,TAB/CAP RE	146	5	13	18
TAMOXIFEN OLL ORALS,LIQ,NON-SPEC L	147	5	13	18
TRETINOIN OSR ORALS,SOL,TAB/CAP RE	157	5	8	13
TRIMETHOBENZAMIDE IAA INJECT,IM REG	158	1	0	1
TRIMETHOBENZAMIDE OSR ORALS,SOL,TAB/CAP	159	1	0	1
TRIMETHOBENZAMIDE RRS RECTALS SYST,SUPP	160	1	0	1
VINORELBINE IAC INJECT,IV REG	165	1	11	12

Table Molforms with Shortages Reported in Years After Study Period

molform number	molform
106	MESNA ACE INJECT,IV REG
16	BUSULFAN ACE INJECT,IV REG
111	METHOXSALEN YAZ ALL OTHERS
152	THIOTEPA ACE INJECT,IV REG
24	CISPLATIN ACE INJECT,IV REG
54	ETOPOSIDE ACE INJECT,IV REG
103	MELPHALAN ACE INJECT,IV REG
112	MITOMYCIN ACE INJECT,IV REG
4	AMIFOSTINE ACE INJECT,IV REG
20	CARMUSTINE ACE INJECT,IV REG
80	IDARUBICIN ACE INJECT,IV REG
84	IRINOTECAN ACE INJECT,IV REG
91	LEUPROLIDE AAA INJECT,IM REG
126	PACLITAXEL ACE INJECT,IV REG
19	CARBOPLATIN ACE INJECT,IV REG
33	DACARBAZINE ACE INJECT,IV REG
39	DEXRAZOXANE ACE INJECT,IV REG
48	DOXORUBICIN ACE INJECT,IV REG
57	FLOXURIDINE ACE INJECT,IV REG
58	FLUDARABINE ACE INJECT,IV REG
74	GRANISETRON ACE INJECT,IV REG
119	ONDANSETRON ACE INJECT,IV REG
133	PENTOSTATIN ACE INJECT,IV REG
163	VINBLASTINE ACE INJECT,IV REG
164	VINCRISTINE ACE INJECT,IV REG
36	DAUNORUBICIN ACE INJECT,IV REG
61	FLUOROURACIL ACE INJECT,IV REG
94	LEUPROLIDE SAZ OTHER SYSTEMICS
144	STREPTOZOCIN ACE INJECT,IV REG
32	CYTARABINE AZ INJECT,OTHER L.A
92	LEUPROLIDE AE INJECT,SUBCUT REG
93	LEUPROLIDE AF INJECT,SUBCUT L.A
110	METHOXSALEN AX INJECT,OTHER REG
14	BLEOMYCIN AG INJECT,MULT ADM REG
97	MECHLORETHAMINE ACE INJECT,IV REG
120	ONDANSETRON IVR INJECT,IV PIGBACK
29	CYCLOPHOSPHAMIDE ACE INJECT,IV REG
31	CYTARABINE AG INJECT,MULT ADM REG
55	ETOPOSIDE DSR ORALS,SOL,TAB/CAP RE
89	LEUCOVORIN AG INJECT,MULT ADM REG
96	LOMUSTINE DSR ORALS,SOL,TAB/CAP RE
104	MELPHALAN DSR ORALS,SOL,TAB/CAP RE
157	TRETINOIN DSR ORALS,SOL,TAB/CAP RE
40	DEXRAZOXANE AK INJECT,INFUSION REG
108	METHOTREXATE AG INJECT,MULT ADM REG
141	SCOPOLAMINE WT INSRT/IMPLANT,TRANSD
142	SCOPOLAMINE DSR ORALS,SOL,TAB/CAP RE
18	CAPECITABINE DSR ORALS,SOL,TAB/CAP RE
109	METHOTREXATE DSR ORALS,SOL,TAB/CAP RE
30	CYCLOPHOSPHAMIDE DSR ORALS,SOL,TAB/CAP
38	DENILEUKIN DIFTITOX AK INJECT,INFUSION
105	MERCAPTOPURINE DSR ORALS,SOL,TAB/CAP RE
131	PEGYLATED LIPOSOMAL DOXORUBICIN AC INJ
136	PROCHLORPERAZINE AG INJECT,MULT ADM RE