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THE LANDSCAPE OF US GENERIC PRESCRIPTION DRUG MARKETS, 2004-2016

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ABSTRACT

Since the 1984 passage of the Waxman-Hatch Act, generic prescription drugs have become central to disease treatment and generic drug entry and price competition has been vigorous in the U.S. Nonetheless, recent policy concern has focused on potential supply inadequacy and price increases among selected generic drugs. Details regarding the supply of generic drugs throughout the product life cycle are surprisingly unstudied. Here, we examine manufacturer entry, exit, the extent of competition and the relationship between supply structure and inflation adjusted prices among generic drugs. Our empirical approach is descriptive and reduced form, following recent innovations on the older structure-conduct-performance tradition. We employ quarterly national data on quantities, wholesale dollar sales and manufacturers from QuintilesIMS National Sales Perspective data, 2004Q4–2016Q3. Defining a market as the molecule-dosage-form, we observe that median sizes of drug markets are predominantly small, with annual inflation adjusted sales revenues of less than $10 million but increasing over time. The median number of manufacturers in each market is about two, the mean about four. We find evidence to suggest decreasing numbers of suppliers over our study period, particularly following implementation of the Affordable Care Act in 2010 and the Generic Drug User Fee Amendments of 2012, attributable both to more exit and less entry. Approximately 40 percent of markets are supplied by one manufacturer; the share of markets supplied by one or two manufacturers is observed to increase over time and is more likely among non-oral drugs and those belonging to selected therapeutic classes. We find evidence to suggest prices of generic drugs are statistically significantly increasing over time, particularly following the implementation of the 2010 Affordable Care Act and the 2012 Generic Drug User Fee Amendments. Price increases are positively correlated with reduced manufacturer counts and alternative measures of increased supplier concentration, holding all else constant. Our results suggest the market for generic drugs is largely comprised of small revenue products the supply of which has tended towards duopoly or monopoly in recent years. Therefore, it is surprising generic drug prices have not been observed to be higher and potentially risen more over our study period. This issue merits further study; we suggest several testable hypotheses based in economic theory.

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I. INTRODUCTION

In the last two decades, a number of developments – changing health insurance coverage, advances in the life sciences, and new regulatory initiatives – have interacted to shape changing trends in various sectors within U.S. health care – hospitals, clinics and physician offices, diagnostics, devices and biopharmaceuticals. The impact of these developments has been especially evident for prescription pharmaceuticals. For example, for decades prescription drugs comprised about 10% of total national health care expenditures, but recent data suggest they now comprise more than 16% of total national expenditures and are expected to rise to comprise approximately one out of every five dollars spent on health care by 2025.[1] Innovation clearly drives some of these trends; the past three decades have witnessed dramatic changes in the availability of drugs effective in treating disease and more is expected in the coming decades.

While much public attention is focused on novel, on-patent "branded" drugs, the generic prescription drug sector has witnessed dramatic changes. On the demand side, the Medicare Modernization Act (enacted in 2003 and implemented in January 2006) increased senior citizen eligibility for prescription drug coverage, thereby increasing the overall demand for prescription drugs. Private prescription drug plans including those administering Medicare's pharmacy benefit have increasingly utilized tiered copayment formularies that incentivize income-constrained beneficiaries to treat chronic conditions with generic drugs.[2] The Affordable Care Act enacted in March 2010 further expanded demand for low cost generic drugs among non-Medicare eligible Americans by providing premium tax credit subsidies to expand commercial insurance access and by expanding the Medicaid program to cover all adults with income below 138% of the federal poverty level. With patient prescription drug copayments for Medicaid and other government programs frequently being zero or nominal,[3] these coverage expansions created additional demand for generic drugs.

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[1] These estimates tend to not count prescription drugs used in the inpatient setting, since hospitals are commonly paid for such care using bundled payment. For estimated and projected national health expenditures 1960-2025 by medical service type see https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html

[2] For discussion, see Duggan and Scott Morton [2010], Duggan, Healy, Morton [2009] and Goedken, Urmie, Farris, Doucette [2010].

[3] In 2013 (2016), 20.1% (26.0%) of all prescriptions dispensed at retail or mail order were for generics with a zero patient copayment, while 3.5% (3.9%) were for brands with a zero copayment. See QuintilesIMS Institute [2017],

On the supply side, in 2011 and 2012 an enormous amount of branded drug spending was jeopardized by the expiration of market exclusivity (the so-called "patent cliff"), creating opportunities for entry and expanded use of low cost generic drugs.[4] Then, in July 2012, as concerns began emerging on the safety and quality of imported generic drugs, Congress enacted the Generic Drug User Fee Amendments ("GDUFA I") as part of the Food and Drug Administration Safety and Innovation Act. This policy committed the FDA to aggressively eliminate its backlog of Abbreviated New Drug Applications ("ANDAs") and complete its reviews of new ANDA submissions in a timely manner.[5]

Together these developments resulted in a massive shift toward generic drugs, whose share of all retail and mail order dispensed drugs increased from 36% in 1994 to 74.5% in 2009 and 87% in 2015.[6] The evolving conventional wisdom involving generic drugs was that extensive entry and price competition among generic manufacturers, facilitated by buying power consolidation among insurers and pharmaceutical benefit management organizations, was resulting in a virtuous circle: increasing access to safe and effective treatments for chronic disease, and ever declining prices, offsetting at least to some extent the higher prices of newly launched and existing branded drugs.[7]

This conventional wisdom began to fade in 2009 as a number of high-profile drug shortages were reported disproportionately involving old, off-patent, largely non-orally formulated drugs. Concerns were raised that perhaps generic profit margins had fallen too low, buying power had become too concentrated, and buttressed by FDA inspections revealing numerous plants were failing to comply with current good manufacturing provisions, manufacturers were not maintaining their production facilities or were even actively exiting these markets.[8] Then in 2012-2013 a sharp trend reversal was first observed with prices of many

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Chart 14, page 20 of 46. For an historic time series of commercial plan generic and brand copayment benefit designs in the U.S., see Berndt and Newhouse [2012].

[4] Aitken, Berndt, Cutler et al. [2016].

[5] For an in depth economic examination of the intent and likely effects of GDUFA I see Berndt, Conti, Murphy [2017].

[6] Berndt and Aitken [2011], IMS Institute for Healthcare Informatics [2016].

[7] Aitken, Berndt, Cutler et al. [2016], Duggan and Scott Morton [2010], Berndt and Aitken [2011] and Frank and Salkever [1997].

[8] On these factors, see Woodcock and Wosinska [2013], Conti and Berndt [2014], Stomberg [2016], U.S. Department of Health and Human Services [2011], and Yurukoglu, Liebman and Ridley [2017].

incumbent generic drugs increasing rather than decreasing,[9] and growing rather than contracting prescription drug expenditures.[10] More recently, lay press reports, government investigations and published studies have documented massive price increases for certain very old drugs that are the standard of care in selected diseases.[11]

These trends raise a key empirical question on which we focus our attention: How competitive are markets for generic drugs, and how has the competitive market structure varied over time and across drug formulations and therapeutic classes? An empirical study of the supply of generic drugs is particularly relevant to U.S. policy now that FDA regulatory changes might have also increased the fixed costs of manufacturing generic drugs and created barriers to entry among generic manufacturers with the July 2012 enactment of GDUFA I. [12,13]

Empirical work on the structure of the generic drug industry has focused almost exclusively on the period leading up to and immediately following generic entry. For example, numerous reports suggest the number of entrants following brand loss of exclusivity ("LOE") increases with the dollar revenue volume of the drug pre-LOE, and that in the 24 months following initial LOE, as the number of entrants increases, average generic prices for molecules decline.[14] While these studies typically focused on oral dosage forms, specialty drugs -- including small molecule drugs formulated as injectables, infusibles and aerosols, physician-administered to patients or otherwise distributed through specialty pharmacies -- are not immune to the forces of generic competition. Conti and Berndt [2015] document significant price declines with the entry of generic cancer specialty drugs, although the average number of entrants into these drugs is observed to be smaller than previously noted among non-specialty drugs. They speculate fewer entrants among these drugs might be related to higher fixed costs and economies of scope in production.

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[9] For discussion of consolidation activities among generic drug manufacturers, see Barrett [2017], Harding [2010], Herrick [2015, 2016] and Silverman [2014b].
[10] See Aitken, Berndt, Cutler et al. [2016] for further details; also see Fein [2013, 2014 a,b,c, 2015 a,b, 2016] and Herrick [2015, 2016].
[11] See, for example, U.S. Department of Health and Human Services, Assistant Secretary for Planning and Evaluation [2016], and the Special Report of the U.S. Senate Special Committee on Aging [2016].
[12] For a more detailed discussion of generic prescription drug manufacturer incentives entailed in GDUFA I, see Stromberg [2016] and Berndt, Conti and Murphy [2017].
[13] For a detailed discussion of GDUFA and its reauthorization as GDUFA II, see Berndt, Conti and Murphy [2017].
[14] See, for example, Berndt and Aitken [2011] and Grabowski and Vernon [1996].

Less is known about the evolution of manufacturer competition years after LOE and generic entry first occurs. Several observers have suggested exploitation of economies of scale and scope from consolidation among generic manufacturers and increased reliance on outsourced contract manufacturers might have reduced the number of entrants and increased the number of molecule exits, particularly among drugs requiring specialized sterile manufacturing capacity.[15] Yet, no empirical work we are aware of has examined generic manufacturer supply over time and characterized manufacturer entry, exit and other measures of competition or compared the robustness of competition in this sector to other health care and non-health care industries. This echoes a notable lack of detailed data to document actual patterns of firm entry and exit in important sectors of the U.S. economy.[16] While the Census Bureau has systematically collected counts of manufacturers and other suppliers across a wide range of products and services, [17,18,19,20,21,22] none of this data provides enough detailed information to identify and count "generic" drug manufacturers distinct from all pharmaceutical manufacturers.[23]

In this research, we characterize the changing landscape of U.S. generic prescription drug markets, 2004-2016, focusing on entry, exit, the extent of supplier competition and two measures of market performance (overall sales revenues and pricing per molecule) using national quarterly data from QuintilesIMS on all national prescription drug sales.[24] Our conceptual framework is based on the traditional structure-conduct-performance paradigm summarized by Tirole [1988], the more recent firm entry and exit literature pioneered by Bresnahan and Reiss [1988, 1991], and health care-specific market structure literature recently summarized by Gaynor, Ho and Town [2015]. Our empirical approach is largely descriptive and reduced form.

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[15] See Woodcock and Wosinska [2013] and Conti and Berndt [2015].
[16] For early work on this topic see McGuckin [1972]; Orr [1974]; Deutsch [1975]; Gorecki [1975, 1976].
[17] https://www2.census.gov/programs-surveys/cbp/resources/2017_CBP_User_Guide.pdf
[18] https://www.census.gov/programs-surveys/economic-census.html
[19] https://www.census.gov/ces/dataproducts/bds/
[20] For a survey, see Dunne, Roberts and Samuelson [1988].
[21] https://www.census.gov/programs-surveys/susb/technical-documentation/methodology.html
[22] See https://www.census.gov/ces/dataproducts/bds/publications.html for a listing of reports and presentations.
[23] including those producing base ingredients or final fill and finished generic and branded prescription drugs.
[24] Dave, Kesselheim, Fox, Qiu, and Hartzema [2017] use 2008-2013 Marketscan™ retrospective claims data to examine prices and market competition for drugs classified as either single or multi-source generic over the entire 2008-2013 time period, but do not consider entry and exit of new brands, or entry of generics following the brand's LOE. The claims data contain mostly retail and mail order pharmacy claims but likely understate sales through other channels such as long term care, hospitals, and federal facilities.

II. BACKGROUND AND CONCEPTUAL FRAMEWORK

The importance of firm entry and exit as determinants of market outcomes such as product price, sales revenues and profits, is well recognized. Theoretical studies have examined the implications of actual, potential and strategically deterred entry, while empirical studies have analyzed correlations among variables measuring market outcomes and factors that hinder entry or hasten exit of producers. A simple two-stage model of firm entry and competition has provided a unifying framework for analyzing the potentially complex relationships among market structure and outcomes across many industries, including empirical studies in anti-trust enforcement, regulatory proceedings, and industrial organization research.[25,26]

Within this tradition, in the short run the number of firms is envisaged as being fixed, with firms competing in product markets via price, quantity and quality choices that generate firm profits for each incumbent as a function of market structure. The level of competition in markets reflects product demand and cost factors including the degree of product differentiation among firms, whether firms compete in prices, quantities or quality, regulatory or other structural factors that may reinforce economic gains to scale or scope and/or facilitate rent seeking. In the long run, the number of firms is viewed as endogenous, resulting from potential entrants each making a decision on whether to enter the market given knowledge and expectations of competition levels and determinants. Beginning with Bresnahan and Reiss [1988, 1991], empirical studies based on this two-period framework have relied on a steady state zero-profit assumptions to semi-structurally or structurally estimate relationships among the number of firms entering and exiting and the nature of price competition in product markets. Within health economics, the empirical approach to estimating relationships among market structure and outcomes tends to remain reduced form (although there are some exceptions), in part due to the presence of health insurance which complicates the usual neo-classical assumptions regarding utility maximization and the nature of demand for medical care inputs and their prices.[27]

[25] On these paradigms, see, for example, Berry and Reiss [2007], Bresnahan and Reiss [1988, 1991], Dafny, Duggan and Ramanarayanan [2012], Dranove [2012], ch. 29 in Scherer [1990], and Scott Morton and Kyle [2012].
[26] See Bresnahan and Reiss [1987, 1991], Berry [1992], Sutton [1991, 2007], and Berry and Reiss [2007].
[27] Gaynor, Ho, Town [2015].

Here we follow the example of previous studies that rely on industry-specific data to examine firm and product entry and exit, but we do so at a more disaggregated level. We define a "product market" by molecule-dosage form that may be manufactured or marketed by multiple suppliers, e.g., atorvastatin tablets marketed as brand Lipitor by Pfizer and as atorvastatin by numerous generic manufacturers.[28] Note that this aggregates over different strengths of the same molecule dosage form, i.e., 10, 20 and 40 mg strengths of atorvastatin tablets marketed by numerous generic manufacturers and by Pfizer as branded Lipitor. Specifically, we quantify the number of firms selling specific molecule dosage forms of generic prescription drugs in the past two decades for sale, and model entry and exit patterns over time conditional on generic industry structure and product characteristics plausibly related to demand, or factors associated with observed levels and trends in firm counts.

To construct these measures, we use a highly detailed, national data source that allows us to count unique suppliers of all prescription drugs sold to U.S. consumers. Furthermore, we use reduced form methods to relate these market characteristics to observed product prices and sales revenues in the cross-section and over time. We assume that in the short-run prescription drug suppliers pursue a non-cooperative, Bertrand pricing strategy with undifferentiated products, resulting in an approximately linear relationship between price and stock and flow measures of supplier counts or concentration measures.[29]

III. METHODS

Data Sources

We obtained quarterly national data on the quantities sold, wholesale dollar sales and suppliers of all prescription drugs approved for sale from QuintilesIMS's National Sales Perspectives™ (NSP) database between Q4 2004 and Q3 2016. NSP data derive from a projected audit covering 100% of the national unit volume and dollar sales in all major classes of trade and distribution channel for U.S. prescription pharmaceuticals. The sample is based on over 1.5 billion annual transactions. NSP provides information on each and every prescription drug by specific chemical and branded names, formulation, dosage and the name of labeler (FDA's

[28] See Schmalensee [1989].
[29] Dunne, Roberts and Samuelson [1988].

terminology for the owner of the New Drug Application or the ANDA in the Orange Book).[30,31] The data derive from an audit of molecule purchases from manufacturers or wholesalers to pharmacies or other distribution outlets, not retail pharmacy sales to patients.[32]

NSP reports "dollar sales" defined as the total amount paid for the purchase of a molecule-dosage-form by quarter. We converted dollar sales into Q1 2016 U.S. dollars using the Gross Domestic Implicit Price deflator.[33] To the extent sales from wholesalers include wholesaler margins and exclude off-invoice rebates paid by manufacturers to pharmaceutical benefit managers and insurers, the NSP data overstate net revenues received by manufacturers.[34]

NSP also reports the volume of "standard units" measuring the number of single items (such as vials, syringes, bottles, or packet of tablets/capsules) contained in a unit or shipping package purchased by pharmacies or other distribution outlets. Standard units are calculated by multiplying the number of units (e.g., 24 bottles) by the product size (50 tablets per bottle).

We excluded all over-the-counter products from the analysis, identified by the NSP variable "rxotl".

Definitions of Measured Variables

The principal units of analyses are, for a given molecule-dosage-form-quarter, its number of standard units sold, its inflation-adjusted sales revenues, its supplier(s) and its inflation adjusted price.

[30] FDA identifies drugs based on NDCs that serve as a universal product identifier for drugs, based on The Drug Listing Act of 1972. FDA publishes the listed NDC numbers and the information submitted as part of the daily updated listing information in the NDC Directory. For a discussion of the FDA's NDC classification system, see U.S. Department of Health and Human Services, Office of Inspector General [2006].

[31] The FDA's Orange Book identifies the applicant of the Abbreviated New Drug Application (ANDA), and notes that the actual manufacturer may differ from the ANDA applicant (also called the labeler) due to outsourcing of manufacturing to contract manufacturers which is common in the U.S. generic drug industry. The ANDA applicant may also differ from the marketer, due to licensing actions. The QuintilesIMS National Sales Perspective data tracks sales from suppliers' invoice data, excluding sales from repackagers and drug compounding organizations. Our use of the term "supplier" should therefore be interpreted as the number of distinct firms selling and marketing a molecule dosage form. For further discussion, see Preface to the 37th Edition of the Orange Book [2017], available online at https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm.

[32] For a discussion of the flow of funds through the various parts of the pharmaceutical distribution system (e.g., manufacturers, pharmaceutical benefit managers, pharmacies, wholesalers, and health plans), see Dusetzina, Conti, Yu and Bach [2017] and Sood, Shih, Van Nuys and Goldman [2017].

[33] https://fred.stlouisfed.org/series/gdpdef/viewdata

[34] For a discussion of rebates, see Aitken, Berndt, Cutler et al. [2016] and Dusetzina, Conti, Yu and Bach [2017].

We identified generic drugs using the following method: NSP contains a data field denoting whether each molecule-dosage form-quarter has "generic, "branded" or "branded generic" patent status. Within the QuintilesIMS classification scheme, "Branded generics" are drugs belonging to the following categories:

(i) Novel dosage forms of off-patent products, often in combination with another molecule. These include line extensions of off-patent products such as those formulated as "extended release" (XR) and "controlled release" (CR). An example of a drug in this category in our sample is Concerta™, an extended release formulation of methylphenidate hydrochloride, the active ingredient in the off-patent drug Ritalin™ commonly used to treat attention deficit hyperactivity disorder.

(ii) On patent with a trade name, but a molecule copy of an originator product FDA approved under an existing NDA. These include drugs for which the formulation is protected by its own patent and/or FDA approved through the 505b2 pathway.[35] An example of a drug belonging to this category in our sample is Proventil™, the albuterol sulfate inhaler used to treat asthma symptoms. The albuterol sulfate active ingredient is no longer patent-protected, but the FDA granted 3-year patent protection to the makers of albuterol inhalers under 505b2 for reformulating with hydrofluoroalkane propellants.[36]

(iii) Off patent drugs with a trade name. Two examples of drugs belonging in this category in our sample are Oxycontin™, a timed-release formulation of oxycodone used to treat pain, and EpiPen, the epinephrine auto-injector for the treatment of serious allergic reactions.

(iv) Off patent without a trade name and commonly manufactured by a single source or co-licensed from the NDA holder. These drugs include sterile hospital solutions.

We combined unit volume and dollar sales of branded generics and generics in all quarters having non-zero quantities and sales revenues sold to create a generic aggregate. Using this approach, we treat alternative dosage forms of the same molecule as distinct product

[35] For a discussion of the 505b2 pathway, see https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf
[36] See discussion by Hendeles, Colice, Meyer [2007].

markets, i.e. famotidine oral tablets or capsules comprise a distinct product market from injectable famotidine formulations.

Among this universe of drugs, the NSP contains two variables denoting "manufacturers": "Corp" and "Mnf". "Corp" is the alphanumeric name of the corporation, including subsidiaries, identified on the sponsor-owned FDA-approved label appearing in the Orange Book (the ANDA applicant), while "Mnf" is the product's manufacturer, such as the "parent" corporation of a multi-corporation firm.[37] We choose to use "Mnf" as the main measure of generic drug supplier and "Corp" as the sensitivity check on "Mnf". We define all supplier measures described below for Mnf and Corp separately.

For each molecule-dosage-form quarterly observation, we count the number of unique Mnfs and Corps having positive unit volume and dollar sales revenue data in that quarter and designate these variables as CountMnfs and CountCorps, respectively:

> NTMnfs/NTCorps$_i$(t) = Total number of manufacturers or corporations supplying molecule-dosage form i in quarter t. This includes manufacturers or corporations that begin to supply i between t-1 and t, which we consider to be "entrants" into the supply of molecule i.

We also create indicator variables called EntrantMnf/EntrantCorp if, immediately following two quarters of zero unit volume and dollar sales, there are at least two quarters of positive volume unit and sales data of the molecule by the Mnf/Corp; similarly, we create indicator variables called ExitMnf/ExitCorp if, immediately following at least two quarters of positive volume unit and sales data, there are at least two quarters of zero volume unit and sales data for the molecule-Mnf/Corp:

> EntrantMnf/EntrantCorp$_i$(t) = number of firms that enter molecule i between quarter t-1 and t.
>
> ExitMnf/ExitCorp$_i$(t) = number of firms that exit molecule i between t-1 and t.

[37] Manufacturers of ANDAs self-identify to the FDA annually on Form 2657.

Note that this definition of Exit likely excludes temporary production cessations, for the Mnf/Corp could still sell from its inventory, generating positive volume unit and dollar sales metrics recorded by NSP in that quarter.

We sum the number of EntrantMnf/EntrantCorp and ExitMnf/ExitCorp and values for each molecule-dosage-form in each quarter to create NEntrantMnf/NEntrantCorp and NExitMnf/NExitCorp:

$$\text{NEntrantMnf/EntrantCorp}(t) = \sum_i \text{EntrantMnf/EntrantCorp}_i(t).$$

$$\text{NExitMnf/ExitCorp}(t-1) = \sum_i \text{ExitMnf/ExitCorp}_i(t-1).$$

We also calculated molecule Herfindahl–Hirschman Indices (HHIs) of concentration by quarter and therapeutic class.[38] HHIs are a commonly-employed indicator of the extent of competition within a specific market and defined time period. These HHIs were constructed using Mnf shares measured in standard unit volume of the molecule-dosage-form sold:

$HHI_{it} = \sum_{NTMnfsi(t)} s_{it}^2$ where s_{it} is the market share of manufacturer of molecule i in time t.

Note that shares are defined between 0 and 100 where the max value is 100 and therefore HHI varies between 0 and 10,000. To facilitate interpretation, note that if the therapeutic class market were on average supplied by two manufacturers (a duopoly) with each supplier having a 50% market share, the HHI would be 5,000; any departure from equal shares would generate an HHI greater than 5,000; for a therapeutic class on average supplied by three manufacturers (a triopoly), equal shares across suppliers would yield an HHI of 3,327, and any departure from each manufacturer having a 33.3% unit share would yield a higher HHI. According to the Department of Justice horizontal merger guidelines, mergers in markets with pre-merger HHIs above 1800 and involving an HHI increase of greater than 100 would likely invite close scrutiny and possibly a challenge by the Department of Justice or the Federal Trade Commission.[39]

To calculate "net" inflation-adjusted prices per unit of molecule markets sold, we divided molecule inflation-adjusted sales revenues by standard units sold in each quarter. The resulting price estimates reflect the actual invoice prices pharmacies, hospitals and clinics pay for the

[38] https://www.justice.gov/atr/herfindahl-hirschman-index. Last accessed last accessed 4 May 2017.
[39] For a discussion of the U.S. horizontal merger guidelines and their enforcement, as well as Scott-Rodino required public notification provisions, see Whinston [2007].

drugs, whether purchased directly from a manufacturer or indirectly via a wholesaler or chain warehouse. Invoice line item discounts are included, but prompt-payment, bottom-line invoice and 340B discounts are not included. Drug rebates paid by the manufacturer to an insurer or intermediary are not reflected in these prices and are not publicly available.[40]

We characterize molecule markets by dosage form and therapeutic class. NSP data for each molecule provides formulation codes to classify drugs into several categories: oral solid tablets or capsules ("oral"); injectable or infusible products ("injectable"); topical preparations; inhaled products, and "other" formulations (e.g. ocular drugs and patches) ("other"). In our analyses, alternative molecule dosage forms serve as a surrogate for differing marginal costs of production.[41]

NSP data for each molecule also contains a slightly modified version of the World Health Organization's 244 four-digit anatomic therapeutic classification (ATCs). We follow QuintilesIMS' own annual reports and report results by molecule therapeutic class using an aggregated classification system related to the general target of biological activity, such as "cardiovascular" or "antineoplastic and immunomodulating". In our analyses, the therapeutic class of a molecule is an implicit proxy for product demand.

Descriptive and Statistical Analyses

We undertake several alternative descriptive and statistical analyses. First, we tabulate the total brand plus generic molecules, manufacturers, corporations, annual revenues, share brand and generic revenues, and revenue share by dosage form, annually 2004-2016 (part-year data for 2004 and 2016 are annualized by extrapolation). We then tabulate the same measures by two-digit therapeutic class, averaged over the study time period. Limiting our focus to generic drugs, we graph the median, mean, and interquartile range of revenues per molecule-manufacturer by study quarter first over all molecules and then disaggregated by molecule dosage form.

Second, we graph the quarterly number and share of manufacturers entering and exiting drug markets over time, separately for brands and generics, and then for generics by dosage

[40] See Dusetzina, Conti, Yu and Bach [2017], and Aitken, Berndt, Cutler et al. [2016].
[41] Previous work by Berndt and Conti [2016] suggests oral molecule forms tend to exhibit smaller marginal costs of production compared to injectables, infusibles, topicals and inhalants.

form. Other things equal, we expect modestly greater numbers and shares of generic entrants over time, as well as numbers and shares of generic exits over time (though perhaps increased exit and decreased entry in the most recent years), and greater number and share exits from markets where the manufacturing technology needed for production is highly specialized (e.g., non-orally formulated molecules), and where GDUFA user fees may also generate fixed costs. Note that this implies an expectation of greater total churn (exit plus entrant) rates over time for generics compared to brands.

Third, we graph the mean, median and interquartile range of the number of generic manufacturers per molecule by study quarter over all molecules and then disaggregated by molecule dosage form. We also plot concentration for generic drugs (measured by HHIs) at the beginning and end of our study time period by therapeutic class. Due to the very large number of blockbuster molecules experiencing LOE and initial generic entry since 2011,[42] we expect concentration measures such as HHI to decline over time, and by greater proportions in therapeutic classes experiencing more extensive patent cliff events.

Fourth, we experiment with a number of simple reduced form regressions. First, at the aggregate molecule level by quarter, we estimate ordinary least square regressions of manufacturer exit and entry shares, separately, as a function of regulatory regime, where for example, a 2% exit share implies a dependent variable measure of 2. We weight our regressions by the number of active manufacturers within each molecule-formulation-quarter. We define four regulatory and insurance coverage regimes: (1) before the Medicare Modernization Act implementation Q4 2004 - Q4 2005 "Pre MMA"; (2) after the Medicare Modernization Act implementation Q1 2006 - Q1 2010 "MMA"; (3) after ACA passage and implementation Q2 2010 - Q3 2012 "ACA"; and (4) after GDUFA I implementation Q4 2012 - Q3 2016 "GDUFA". We estimate these models including controls for drug characteristics, quarterly time passage and molecule fixed effects. We expect entry to increase in both the ACA and GDUFA regimes, given the ACA's market expansion and the large number of blockbuster drugs experiencing LOE that create opportunities for entrants, and we expect exits to increase in the ACA and GDUFA

[42] For a list by year of generic drug approvals see U.S. Food and Drug Administration, "ANDA (Generic) Drug Approvals – Previous Years," available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm050527.htm.

regimes, given that the patent cliff creates opportunities for generic manufacturers to shift production from old, mature generics to newly genericized molecules, and because of incentives to exit brought about by the GDUFA user fees.

Fifth, we estimate molecule price levels on the log scale as a function of regulatory regime, drug characteristics, counts of manufacturers or corporations supplying the molecule and alternative measures of manufacturer concentration (HHI). Here we examine the pricing trajectory of generic drugs over time, the responsiveness of their prices to regulatory regime, and differences in price levels as a function of drug characteristics. Our dependent variable is defined at the molecule-formulation-time level taking the log of the average price per standard unit and estimated standard errors are clustered at the molecule market level. We expect pricing levels to be higher for non-oral generics compared to oral generics due in part to their higher fixed costs of production, holding all else constant. We expect pricing to be responsive to manufacturer counts and concentration both between and within molecule, with prices increasing in concentration and decreasing in manufacturer counts, holding all else constant.

RESULTS

Descriptive statistics

Putting the U.S. generic drug industry into context**,** in **Table 1** we report descriptive statistics of our sample of brand and generic manufacturers and molecule markets by year. Approximately 500-650 manufacturers are in our data between 2004 through 2016. The count of manufacturers increases roughly linearly over time. As expected, the number of corporations in all years is slightly smaller than the number of manufacturers (average difference 123 over study period) but tracks manufacturers in trend. These manufacturers/corporations sold approximately 1700 to 2250 unique molecule-dosage-form products, with the number of molecule-dosage-forms increasing at a decreasing rate over our study period. Total inflation-adjusted annual sales revenue derived from these molecules by these manufacturers ranged (over both brands and generics) from approximately $295 billion in 2004 to $447 billion in 2016. Brands comprise a larger share of annual sales revenue compared to generics in all years, but they decrease in importance over time from 83% of annual sales revenue in 2004 to 74% of annual sales revenue in 2016. While orally formulated generics comprise the largest category of generic sales revenue in all years, this share declines from 67% in 2004 to 49% in 2016. At the same time, injectable

and other formulated generic drugs become increasingly important to annual sales revenue: injectable sales revenue increase from 23% of total in 2004 to 38% in 2016 and other sales revenue increases more modestly from 10% in 2004 to 13% in 2016.

Table 2 reports descriptive statistics of our sample by therapeutic category over the study period. Interestingly, there is significant variation in both counts of manufacturers/corporations and counts of molecules by therapeutic class. Most therapeutic classes have between 100 and 300 manufacturers (B= blood and blood forming organs, C= cardiovascular system, D= dermatologicals, G= genito-urinary system and sex hormones, H= systemic hormones excluding sex hormones, J= anti-infectives for systemic use, L= antineoplastic and immunomodulating agents, N= nervous system, R= respiratory system, S= sensory organs and V= various), some therapeutic classes appear to have fewer than 60 manufacturers or corporations (K= hospital solutions and T= diagnostic agents) and a handful have larger than 300 (A= alimentary tract and metabolism, and M= musculo-skeletal system). In terms of average annual revenues, the largest therapeutic class is N= nervous system with about $53 billion, followed by A= alimentary track and metabolism at about $44 billion, L= antineoplastic and immunomodulating agents at about $43 billion, M= musculoskeletal system at almost $40 billion, and J= anti-infectives for systemic use and C= cardiovascular disease at about $39 billion annually. By contrast, for K= hospital solutions, average annual revenues are relatively tiny at just under $363 billion. Significant variation occurs among therapeutic classes in branded revenue share ranging from 4% in K= hospital solutions to over 90% in L= antineoplastic and immunomodulating agents and almost 90% in T= diagnostic agents. Similarly, there are significant revenue share variation across therapeutic class by molecule formulation. In some therapeutic classes, generic drugs are largely non-orally formulated (B= blood and blood forming organs, D= dermatologicals, H= systemic hormones excluding sex hormones, K= hospital solutions, L= antineoplastic and immunomodulating agents, M= musculoskeletal system, R= respiratory system, S= sensory organ molecules, and T= diagnostic agents) or "other" formulated (D= dermatologicals, R= respiratory system and S= sensory organs molecules).

Figure 1 reports our first set of results -- mean, median, and interquartile range of quarterly revenue per generic molecule-dosage form-manufacturer sold (note that brands are excluded from this figure). While median quarterly sales revenues are approximately $100K in the early years of our study ($400K per year) and double to approximately $200K in the 3rd

quarter of 2016 ($800K per year), the 75th percentile of quarterly sales revenue per molecule-manufacturer is approximately $1 million in the early years of our study ($4 million per year) increasing to approximately $1.5 million in the 3rd quarter of 2016 ($6 million per year). Although median quarterly revenue per molecule-dosage-form-manufacturer appears to be approximately stable between 2004 and 2013 and then appears to rise starting around 2014, the 75th percentile of revenue per molecule–manufacturer increases sharply in 2012, a year in which the "patent cliff" was substantial, and a number of authorized generics experienced 180-day exclusivity. The 25th percentile is relatively stable at less than $50K per quarter ($200K per year). Most striking, however, is that in every quarter, the mean revenues per molecule-dosage form-manufacturer is several times larger than the 75th percentile number, indicating that sales revenues per molecule-manufacturer are extremely skewed. In the early years of our sample, mean quarterly revenues were about $3 million per quarter, about three times larger than at the 75th percentile, while by the end of the 2004-2016 time period mean quarterly revenues were about $4 million, still much larger than the approximately $1.5 million at the 75th percentile. Hence, although the vast majority of molecule–dosage form-manufacturer sales revenues per quarter are less than $1.5 million ($6 million annually) in 2016, a small number of much larger sales revenue molecule-dosage form-manufacturer markets raise the quarterly mean to about $4 million ($16 million annually).

We also report these statistics by molecule-dosage-form (**Figures 2, 3** and **4;** note the use of different vertical scales in these figures). In all years injectable or infusible molecules (**Figure 3**) exhibit larger median, mean and 75Th percentile sales revenue per manufacturer compared to oral (**Figure 2**) and other dosage form products (**Figure 4**). Molecule dosage forms in the other category exhibit a different periodicity of revenue -- stable or falling through 2013 and then dramatically increasing beginning in late 2014. Therefore, the aggregate trends in sales revenue per molecule-manufacturer reported in **Figure 1** appear to be driven by orals and injectables. However, in all three dosage forms, sales revenues per molecule-manufacturer are highly right-skewed, with the difference between mean and median being the largest in the other formulation.

Figures 5 through **Figure 8** report our second set of findings, now focused on generic manufacturer-molecule-dosage-form entry and exit patterns between 2004 and 2016. We find different entry and exit patterns over time, and notably document decreased entry and increased exit in the most recent time periods. **Figure 5** reports the quarterly number of manufacturers of

molecules newly entering in our study sample over time on the left y-axis and the share of entering manufacturers of molecules as a percentage of total active manufacturers-molecule pairs in our study sample over time on the right y-axis (note that 2 on the right vertical scale is 2%), aggregated over dosage forms. The number of entrants increases from about 150 per quarter to just under 300 per quarter in 2013Q1 (close to the implementation of GDUFA I), and then falls back to about 175 through 2016. Expressed in percentages, entrant share increases from about 2.5% to about 3.75% between 2004 and early 2013, and then falls to about 2.0% in 2015-2016.

Figure 6 plots the number of exits and share of incumbents exiting the molecule-generic manufacturer-dosage-form market over time. Here, the time trend for product exits differs sharply from that for product entrants. Unlike entrants whose numbers and share generally increased up to late 2012 and then sharply decreased, for exits the number generally increases over time from about 100 in the early quarters, peaking at about 210 in 2011Q2 and again in 2014Q2 and 2015Q1. Note that the first observed exit peak occurs in 2011, just before the patent cliff. Also of note is that while the number and share of exits fell after the 2011 peak, both exit measures were still larger than in the 2004-2007 time frame so that the overall time trend is one of increasing exits over time.

By comparing numbers and shares in **Figures 5** and **6** we find that in all quarters through 2014, the number and share of entrants is larger than the number and share of exits, but after 2014 they tend to converge. In particular, the number (share) of new manufacturer entrants is about 150-200 (2.3-3%) between 2004 and 2012, increases to 270 (3.8%) in the first quarter of 2013 and then falls (in number to about 175, in share to 2%). Both the number and the share of new manufacturers exhibit similar periodicity in their changes over time, suggesting stability in the net number of manufacturers. Total quarterly exit plus entry churn rates are relatively stable over the study period at about 4.5%, but the entry vs. exit composition shifts. Interestingly, manufacturer exits are about 100 (1.5%) between 2004 and 2007 and then increase to approximately 150-200 (2-2.6%) beginning in 2008 and continuing to increase thereafter, although not linearly.

Figures 7 and **8** graph generic entry and generic exit share, respectively, by molecule formulation over time. Here the numerator of the share is the number of unique molecule market-manufacturer pairs by formulation entering or exiting U.S. supply (e.g. oral entrants or

exits) and the denominator is the number of incumbent manufacturers by formulation. As seen in **Figure 7**, although there are a few outliers, in general the generic entry share for oral and injectable dosage forms ranges from just under 2% to 4%, while that for other dosage forms is occasionally greater than 4%, and spikes at 7% in 2013Q1.

As seen in **Figure 8**, generic exit share by molecule formulation is more variable and more volatile over time than entry share. In particular, in most quarters but not in late 2013 -- early 2014, the generic injectable exit share is less than that for oral and other forms. Until about 2013, the oral generic exit share is larger than that for injectable and other generic dosage forms, and since 2013 oral and injectable generic exit shares have converged. While the exit share for other generic dosage forms was generally in between that of oral and injectable generic dosage forms until 2014, beginning around 2014 the other generic drug exit share increased several fold, from around 2% to between 3% and almost 6% in 2015.

Thus while for both exits and entrants the aggregate generic share over all molecule dosage forms was relatively stable over the 2004-2016 study period, abrupt movements in the exit and entry share of "other" dosage forms have contributed to increased volatility in the latter part of the study time period.

Figure 9 compares manufacturer entry share over time between drugs by patent status. As expected, we observe more entrants among generics including branded generics compared to brands throughout the study period. While the share of generic entrants falls beginning in late 2012, the share of branded entrants is larger post-2012 than earlier, and in the latter years of the study time period the difference between brand and generic entry shares is much smaller than earlier. Total brand plus generic entry share falls from about 6% in 2004 to about 4% in 2016.

Analogously, **Figure 10** compares manufacturer exit share over time between drugs by patent status. Generic exit share increases irregularly between 2004 and 2011 from about 1.5% to about 3%, and then falls to about 2.5% after 2011. For brands the time trend in exit shares is on balance falling, averaging about 1% over the entire time period, but exit shares spike upward in 2008-2009, then fall to a low of less than 0.5% in 2012, and increase slowly to about 1.3% since then.

A third set of results we report begins with **Figure 11,** which graphs the mean and interquartile range of manufacturer counts per generic molecule by quarter during the study

period (note this figure only includes generic drugs). What we observe is that the number of manufacturers per molecule dosage form is surprisingly small, implying that competition is limited. In particular, the median number of manufacturers per molecule dosage form ranges between 2 and 3 prior to 2008 and then falls to 2 after 2008. Interestingly the 75th percentile of manufacturer counts of generic drugs is stable at 5-6 throughout the study period, while the mean increases modestly from about 4.6 to about 5.0 between 2004 and 2016. Unlike what we observed for revenues per molecule-manufacturer-dosage form in **Figures 1** through **Figure 4**, where the mean was much larger than revenues at the 75th percentile, for number of manufacturer counts per molecule dosage form the mean is larger than the median, but the mean is less than the value at the 75th percentile. Hence, while number of manufacturer counts is right skewed, it is much less so than is the case with revenues per manufacturer-molecule market, suggesting that the outlier revenue molecule per manufacturer product markets are likely occurring in markets with a small number of manufacturers.

Figures 12, 13 and **14** report manufacturer per molecule counts by molecule dosage form among generic and branded generic molecules only. In all quarters, the median number of manufacturers of injectable drugs remains constant at 2; the median number of oral drugs ranges between 2-3 with a decrease observed in 2009-2012 and then a recovery to 3 in 2013; the median number of manufacturers of other generic drugs is initially 1 but increases to 1.5 or 2 in 2013 and thereafter. For all dosage forms, means always lie below the 75th percentile values but above the median. For orally formulated molecule markets, means gradually increase over time from just over 5 to almost 6, for injectables the mean is stable at about 2.6 to 2.7, while for molecules in the other formulation category the mean is generally falling over time from about 3.2 to about 2.8. In summary, the mean count of manufacturers per molecule of about 5 to 6 is about twice that for injectable and other forms, both of which are about 2.8 towards the end of our study time period.

The final set of results we report concerns the concentration of generic and branded generic molecule markets which we quantify using two separate metrics. First, we examine the share of generic drugs supplied by 1, 2 3 and 4 or greater manufacturers over the study period and by dosage form. **Figure 15** documents that approximately 39-40% of generic drug molecule dosage forms are supplied by only one manufacturer and that that percentage grows to about 44% in early 2011, after which it falls back to about 40%. The share of molecules supplied by

two manufacturers grows over the study period as well from just about 11% to 13%, implying that the share of generic molecule dosage forms supplied by one or two manufacturers increases from just under 50% in 2004-2005 to just over 50% in 2016. Although the share of molecules supplied by four or more suppliers decreases from about 40% to 39%, the share supplied by three molecules decline slightly from about 9% to 8% between 2004 and 2016. An alternative perspective emphasizes stability, noting that over the entire 2004-2016 time period, the share of generic molecule dosage forms manufactured by one or two suppliers has remained relatively constant at about 50%.

Figures 16, **17** and **18** repeats these calculations by generic drug dosage form. Comparing across drug formulations, we find that "other" formulated drugs and injectables and infusibles are in every quarter more likely to be supplied to the U.S. market by 2 or fewer suppliers compared to oral generic drugs. Furthermore, the share of drug product markets in both oral and non-orally formulated categories supplied by two or fewer manufacturers grows over our study period; this trend appears more pronounced among non-orally formulated drugs.

An alternative way of quantifying market concentration is by computing the Herfindahl Hirschman Index (HHI) metric in unit volume shares among generics by therapeutic classes. **Figure 19** plots manufacturer concentration among only generic drugs by molecule therapeutic class in Q2 2005 (the "early period" on the horizontal axis) and in Q1 2016 (the "late period" on the vertical axis). Classes above the 45 degree dotted line have increased concentration over time, while those below that line represent decreased concentration over time. While molecules belonging to numerous therapeutic classes became less concentrated over our study period (e.g., C= cardiovascular system, N= nervous, H= systemic hormonal excluding sex hormones, L= antineoplastic and immunomodulating agents, M= muscolo-skeletal system, J= antiinfectives for systemic use, S= sensory organs, and G= genito-urinary system and sex hormones), others became more concentrated including K= hospital solutions and V= various. A number of therapeutic classes did not experience any substantial change in manufacturer concentration during the study period, including molecules in the following classes: A= alimentary tract and metabolism, B= blood and blood forming organs, D= dermatologicals, T= diagnostic agents, and R= respiratory system agents. Note that while concentration as measured by the HHI is generally decreasing over time, as shown on the vertical axis, for most therapeutic classes HHI concentration is far above 5,000. In only two therapeutic classes, N= nervous system and H=

systemic hormones excluding sex hormones is the HHI less than or slightly larger than 5,000 in Q1 2016. Thus, concentration among manufacturers appears to have declined over time in most therapeutic classes, yet generally concentration among manufacturers of generic drugs is very high and above Department of Justice horizontal merger guideline thresholds.

In summary, U.S. generic molecule markets typically generate rather modest annual revenues, have a small number of competitors, and are highly concentrated. Concentration of suppliers appears either rather stable, or by some measures to be growing over time especially among non-orally formulated generic drugs and among select therapeutic classes.

Reduced form regression results

We have also undertaken several preliminary multiple regression analyses. **Table 3** reports the results of regressions of share of manufacturers exiting as a function of regulatory regime, drug characteristics, time and the interaction of time passage and drug characteristics where we limit the sample to generic and branded generic molecules and exclude brands. To save on space, we suppress standard error estimates in this and subsequent tables, and cluster all of our standard errors at the molecule level. In the Pre-MMA period, the share of manufacturers exiting is about 1.552% (the constant term plus the pre-MMA coefficient in Column 1); during the MMA period, the exit share increased to 1.891% (1.552 + 0.339), after MMA and during the ACA period the exit rate increased to 2.368% (1.552 + 0.816), and since GDUFA implementation in 2012Q4 it fell slightly to 2.306% (1.552 + 0.754). Manufacturer exits are estimated to increase over time by 0.025 percentage points each quarter in the data (Column 3, time trend coefficient). After controlling for molecule formulation and therapeutic class (Column 2), the effect of regulatory regime passage, notably the ACA (0.948 percentage points) and GDUFA implementation (0.896 percentage points) compared to Pre-MMA levels appears to have a statistically significant positive effect on manufacturer exit share. Exit rates are higher among oral formulations (0.494 percentage points) and injectables (0.199 percentage points) compared to other formulation types (Column 3). Finally, columns 4 and 5 demonstrate the heterogeneity in time trends of the exit share across therapeutic category and formulation type.

Table 4 reports results of repeating these regressions for manufacturer entry share into molecule markets as a function of regulatory regime, drug characteristics, time and the interaction of time passage and drug characteristics where the sample is limited to generic drug

molecules. Base level entry share of manufacturers into molecule markets amounts to 3.076% in the Pre-MMA period (constant term in Column 1 plus Pre-MMA coefficient) and is about twice that observed for exits (1.552% in **Table 3**). However, compared to Pre-MMA levels, manufacturer entry decreases over time by 0.014 percentage points each quarter in the data (Column 3, time trend coefficient). We also estimate declines in entry after MMA implementation amounting to 0.251 percentage points and after GDUFA passage amounting to 0.431 percentage points (Column 1) compared to the Pre-MMA period. Less entry also occurs among injectables (0.406 to 0.466 percentage points, Columns 2,3,4) compared to other formulated molecule markets. More entry occurs among orals (0.313 to 0.370% more) compared to other formulated molecules (Columns 2-4) holding all else constant. There is considerable variation in average entry rates across therapeutic classes (Columns 2-5), and among therapeutic class specific time trends (Column 4). The formulation specific time trend in entry rates is declining for all three molecule formulation categories but is declining noticeably faster for "other" formulations compared to injectable or oral formulations (Column 5).

Note that in terms of regulatory regime, while entry rates during the ACA and GDUFA time periods are falling relative to the pre-MMA era (column 1 of Table 4), exit rates during the ACA and GDUFA regimes are increasing relative to the pre-MMA era (column 1 of Table 3). With entry rates declining and exit rates increasing during these most recent time periods, the decline in concentration may be decelerating, or may even be reversed with concentration increases. This raises issues concerning the impact of concentration on generic drug prices, to which we now turn our attention.

Table 5 reports results of regressing log of price level as a function of regulatory regime, log corporation or log manufacturer counts and drug characteristics among generic and branded generic molecules. Column 1 includes regulatory regime fixed effects. In the Pre-MMA period we estimate generic molecule price levels to be $0.926 per standard unit (exp^-0.082 in Column 1). Prices increase after MMA implementation, increase further following ACA implementation, and again after GDUFA implementation (Columns 1 and 2) compared to the Pre-MMA period. Of greater interest is the association between prices and concentration. A robust finding is that the estimated elasticity of price with respect to corporation count ranges from -0.735 to -0.803 (Columns 2 through 6), while the estimated elasticity of price with respect to manufacturer count is very similar, ranging from -0.710 to -0.777 (Columns 8 - 12). Assuming an estimated

elasticity of -0.75, a log change from three to two manufacturers is equal to -0.4955 log units, implying a predicted price increase of -0.75x-0.4955 = 0.3716, or about a 37% price increase. It is important to note that when we add fixed effects for molecule (Columns 7 and 13) the impact of corporation or manufacturer count on price remains negative in sign, statistically significant, but their estimated effect size is approximately halved. Therapeutic classes are observed to exhibit large between class price variability. For example, therapeutic classes with high prices (compared to those in the excluded class A= Alimentary class) include: L= antineoplastic and immunomodulating agents, T= diagnostic agents, J= anti-infectives for systemic use and K= hospital solutions (Columns 4 and 10), holding all else constant.

Finally, **Table 6** reports results of regressing log of prices as a function of the log of manufacturer concentration (log HHI), drug characteristics, regulatory regime and time passage among generic drugs only. Pre-MMA prices per standard unit of generic molecules are observed to be approximately a dollar. We also find increasing manufacturer concentration is associated with statistically significant greater prices for generic drugs in all specifications (Column 2 - 7); a 1% increase in the HHI manufacturer consolidation measures is associated with a 0.843 to 0.963 percentage point increase in price (Columns 2 - 7). Also notable are the coefficients on drug characteristics and manufacturer concentration: holding all else constant, the prices of injectable and other formulated generic molecules are more responsive to increasing manufacturer concentration (Columns 8 - 12), even when controlling for molecule fixed effects (Column 13).

SUMMARY AND DISCUSSION

In this study, we have examined entry, exit, the extent of competition and relationships between industry structure and selected measures of market performance among all prescription drugs in the U.S., using QuintilesIMS National Sales Perspective data, 2004Q4 – 2016Q3.

Approximately 500-650 manufacturers supplied prescription drugs between 2004 and 2016, with the count of manufacturers increasing steadily over time. These suppliers sold approximately 1700 to 2200 unique molecules, as the number increased at a decreasing rate over the study period. Total annual sales revenue derived from these molecules by these brand and generic manufacturers increased substantially over time, from approximately $300 billion in 2004 to $450 billion in 2016. Brands comprise a larger share of annual sales revenue compared

to generics in all years, but brands decrease in importance over time from 83% of annual sales revenue in 2004 to 74% in 2016.

We have four sets of important, novel findings on the supply of generic drugs in the U.S. First, quarterly sales revenues per quarter for a typical manufacturer-generic drug are surprisingly small: Median quarterly sales revenues are approximately $100K in the early years of our study ($400K annually) and double to approximately $200K in the 3rd quarter of 2016 ($800K annually). The 75th percentile of quarterly sales revenue per molecule-manufacturer is approximately $1 million in the early years of our study ($4 million per year) and increases to approximately $1.5 million in the 3rd quarter of 2016 ($6 million per year). However, these revenue data are extremely right skewed, with the mean values almost three times larger than the 75th percentile values. When paired with other research documenting that the number of distinct molecules for which the sponsor has an approved ANDA is typically five or less,[43] this research suggests that the U.S. generic drug industry is populated by numerous relatively small firms, with each of their small product portfolios capturing modest annual revenues. However, for a small number of generic products and firms, revenues are much greater. We suspect this latter category of generics drugs is largely comprised of generics having 180 day exclusivity, "authorized generics" -- those manufactured by or licensed from the branded drug holder -- and a select number of branded generics,[44] although more research into this skewness is warranted.

A second set of findings concerns entry and exit numbers and rates, which have differing time trends. The number of entrants and the entry rate increased to about 2013, but have declined since then. By contrast, the number of exits and the exit rate have generally increased over time. While entry numbers and entry rates are generally greater than exit numbers and exit rates, the difference between them has decreased in recent years. Why the number of exits is generally increasing over time merits further study, but we note this finding is consistent with the observed decline in the number of active pharmaceutical ingredient (API) and final dosage form

[43] See Berndt, Conti and Murphy [2017].
[44] On 180 day exclusivity, see Berndt and Aitken [2011]. A detailed description of the availability, prices and revenue generated by authorized generics may be found in Federal Trade Commission, "Authorized Generic Drugs: Short-Term Effects and Long-Term Impact", An Interim Report" [2011], A list of authorized generic drugs supplied to the U.S. market and maintained by the FDA is available at https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm126389.htm.

(FDF) manufacturing facilities reported in Berndt, Conti and Berndt [2017] based on manufacturer-supplied data from the FDA.

A third rather surprising result is that the median number of manufacturers producing in a molecule market is between 2 and 3 up until 2007, and is 2 thereafter.[45] The 25th percentile is 1 manufacturer, and the 75th percentile is 5-6 manufacturers. We find evidence to suggest decreasing numbers of generic drug manufacturers over our study period, particularly following implementation of the Affordable Care Act and GDUFA I, attributable both to more exit and less entry over time. Furthermore, the share of generic drugs with only one manufacturer is approximately 40 percent and has grown over time; non-orally formulated generic drugs are much more likely to be supplied by 2 or fewer manufacturers than are oral generic drugs. Hence, we conclude that U.S. generic drug markets should be considered in steady state to typically involve only a small number of competitors. This conclusion contrasts rather sharply with evidence presented by previous authors suggesting that generic competition is significant, commonly involving four or more suppliers, in the first 24 months after loss of patent protection.

The fourth set of important findings we report is that while market concentration as measured by the HHI has generally declined between the beginning and end of our study time period, even in 2016Q2 in 13 of the 15 therapeutic classes we examined, average HHIs were over 4,000 -- a level far above Department of Justice and Federal Trade Commission thresholds for generating scrutiny of any consolidation activities. Only in two of the 15 therapeutic classes (nervous systems, and systemic hormones excluding sex hormones) was the 2016Q2 HHI concentration metric less than or slightly greater than 5,000.

We also present evidence documenting inflation-adjusted prices of generic drugs have increased over time and are inversely associated with limited supply competition in molecule-dosage form product markets. These results are consistent with media reports of large prices of certain "sole source" or "branded-generic" drugs.[46,47,48]

[45] Although their research is based on a different data set restricted to molecules being either single-source brand or multi-source generic throughout the 2008-2013 time period, Dave, Kesselheim, Fox et al. [2017] have recently reported similar limited number of competitor findings in U.S. prescription pharmaceutical molecule markets.
[46] See discussion by Rockoff [2016].
[47] See discussion by Silverman [2014a].
[48] For details see U. S. Department of Health and Human Services, Assistant Secretary of Policy and Evaluation, [2016].

Our findings have several implications. First, we are intrigued by the implication of our findings that many generic drug markets in the U.S. are supplied by monopolists. Some therapeutic classes and molecule formulations appear to be long characterized by this market structure. With such limited suppliers of generic drugs observed over our study time frame and high levels of concentration, we wonder why prices of generic drugs and associated revenues have not risen more dramatically over time than we have observed. This issue clearly merits detailed further inquiry. Here we briefly offer several hypotheses.

One hypothesis is that with a small number of direct wholesaler purchasers, pharmaceutical benefit management firms (PBMs) and group purchasing organizations, competition among the small number of suppliers of each molecule is intense due in large part to the fact that it resembles undifferentiated Bertrand competition, where prices are close to marginal costs in spite of there being only a small number of competitors.[49] We wonder whether the increasing shift towards the use of generic drugs accelerated by consolidation among PBMs and downstream purchasers whose buying power, utilization management tools and ability to play generic manufacturers off against each other, has helped to establish and maintain downward pressures on generic drug prices. The intensity of price competition among generics is likely more intense than that among branded drug prices in numerous therapeutic classes with multiple alternative therapies.[50]

A related hypothesis is that many generic molecule markets (particularly among oral formulations) are contestable. In a contestable market, firms hold an option to enter, facilitated by minimal entry (and exit) costs on short notice. When markets are contestable, even if there are only a small number of actual suppliers, the prices of the products and associated revenues may more closely resemble those resulting from competitive markets compared to monopolies or duopolies.[51] One institutional characteristic hindering contestability in the U.S. is the entry cost

[49] For further discussion of this competition, see Berndt, McGuire and Newhouse [2012] and Berndt and Newhouse [2011].

[51]Contestable markets and their implications are discussed in, inter alia, Economics Online [2017]. Note that recent widely publicized price increases for very old drug molecules apparently occurred in cases where no previously exited manufacturer still owned an approved ANDA, and thus barriers to entry were very high, i.e., the market was not contestable. See U.S. Senate Committee on Aging [2016] for further details on these markets.

of obtaining an ANDA – whose direct costs have been estimated to be in the range of $1 - $5 million.[52]

However, for those firms holding an ANDA but having temporarily exited the market, the threat of reentry might credibly facilitate contestability. Specifically, the threat of reentry could act to discipline incumbents' pricing behavior, for if prices were to increase far beyond competitive levels the temporarily exited manufacturer may choose to reenter.

This raises the question of how costly generic drug market discontinuation or complete withdrawal are.[53] Although sometimes used interchangeably, product discontinuations and product withdrawals are two distinct actions. With either a letter to the FDA or the filling out of a form, the ANDA holder can inform the FDA that it will be discontinuing the marketing of a product. The discontinuation can be temporary or indefinite. The holder continues to hold the ANDA while the product is discontinued and can inform the FDA at a later date that it will resume marketing the product. What the FDA will require of the ANDA holder before it can resume marketing legally depends on, among other things, the duration of the discontinuation, and the extent to which new manufacturing facilities and marketing activities will differ from pre-discontinuation. If under resumed marketing the manufacturing process will be altered considerably and be at a new facility, or involve a new formulation, the FDA may require an inspection and perhaps even approval of a prior approved supplement. If the duration of the discontinuation is short and there is no meaningful change from pre-discontinuation manufacturing and marketing activities, then marketing can resume with little delay, need for inspection or other formalities. Under GDUFA I, even if the discontinuation involved closing an entire active pharmaceutical ingredient (API) or final dosage form (FDF) manufacturing facility, the ANDA holder would continue to be assessed annual API and FDF facility fees during the duration of the discontinuation period. Under the proposed 2017 reauthorized Generic Drug User Fee program (GDUFA II), the ANDA holder pays an ANDA Holder Program Fee while the product is discontinued, but there are ways in which this annual carrying cost can be

[52] See Berndt and Aitken [2011] for references estimating generic ANDA entry costs.
[53] We are indebted to Mr. Kurt Karst of Hyman, Phelps and McNamara PC for helpful discussion on these definitions and issues, but are solely responsible for any errors or inaccurate interpretations.

minimized.[54] Note that under GDUFA II, the annual cost to a firm of indefinitely discontinuing marketing a product could be quite low, and much lower than under GDUFA I.

In contrast to a discontinuation, an ANDA holder can inform the FDA it is withdrawing the product. Withdrawal is permanent, and implies that the FDA's approval of the initial ANDA is rescinded. Under both GDUFA I and GDUFA II, no annual user fees are assessed on withdrawn ANDAs. After accumulating a number of withdrawn ANDAs, the FDA typically publishes a list of withdrawn products in the *Federal Register* and in the "Additions/Deletions for Prescription Drug Product List" in its periodic issues of the Orange Book, but in that list it does not distinguish discontinued from withdrawn ANDAs. Hence, based only on Orange Book information, a potential entrant cannot distinguish between withdrawn and discontinued ANDA products, although the identity of withdrawn products might be obtained by scavenging through *Federal Register* announcements.

What do these provisions imply for reentry costs that might support the existence of contestable generic drug markets? Note the option value cost of withdrawal is much larger than that of discontinuation since the former requires a new ANDA. Regarding discontinuation, under GDUFA II, the annual costs of hibernating are smaller than under GDUFA I -- under GDUFA I the annual API and FDF facility fees could be substantial. Under GDUFA II, the annual ANDA Program User fees could be mitigated by parking the ANDAs in a repository (see previous footnote). Under both GDUFA I and GDUFA II, the height of reentry barriers depends on the duration of the discontinuation and the need to alter post-discontinuation from pre-discontinuation manufacturing and marketing activities. For incumbent manufacturers, the extent to which potential entrants could discipline incumbents' incentive to increase prices would depend on how much information the incumbent had regarding which ANDAs were withdrawn vs. discontinued, and for discontinued ANDAs, how long since the discontinuation occurred and how radically different would manufacturing be post-discontinuation from pre-discontinuation.

[54] In the 28 June 2017 FDA Blog, "ANDA Arbitrage & the New ANDA Holder Fee Under GDUFA II", Kurt Karst writes how a company called ANDA Repository LLC could temporarily "park" discontinued ANDAs and pool them so it took advantage of lower per-ANDA annual fees for ANDA sponsors holding 20 or more ANDAs, and then returned control of the ANDA to the original ANDA holder when it wanted to resume marketing). FDA publishes the cumulative list of discontinued products in a cumulative supplement "Additions/Deletions for Prescription Drug Product List" in its periodic issues of the Orange Book.

Although the semblance of the generic drug industry under GDUFA I and GDUFA II merits additional study, based on this preliminary analysis we conclude that the U.S. generic drug market does in fact have some likeness to a contestable market, but the semblance likely varies considerably across the various molecule-dosage-form markets and over time related to regulatory regime. How this limited likeness to contestable markets has interacted with demand shifts due to undifferentiated Bertrand price competition in the presence of highly concentrated buying power from wholesalers, PBMs and pharmacy chains and, in turn, impacted generic price setting are very important issues inviting further theoretical and empirical research.

A third implication of our findings is that while the Waxman-Hatch Act is founded on the assumption of the desirability of establishing competition through lowering initial entry costs, less policy focus has been placed on the long-term maintenance of competition in generic prescription drug markets. Over time, several forces may act to erode the latter. Alleged anti-competitive activities among generic manufacturers and between generic and branded firms include raising entry barriers by, for example, "pay for delay" agreements.[55] Our results provide suggestive evidence that federal policies in pursuit of worthy goals, including ACA and GDUFA I, might have inadvertently eroded generic competition through increased user fees that increased entry barriers and incentives to exit.[56] Some observers have considered the FDA's increased intensity of inspecting foreign and domestic manufacturing sites for compliance with good manufacturing practices as contributing to plant closings and drug shortages.[57] Future research should more closely examine the intended and unintended effects of these and other policies on generic drug competition.

Antitrust policy is but one long established tool expressly aimed at maintaining competition in consumer product markets. An important issue raised by our findings is the adequacy of the current Hart-Scott-Rodino $80.8 million minimum threshold for required pre-merger public reporting of acquisition transactions to the Federal Trade Commission and Department of Justice.[58] We find here that generic molecule markets typically involve less than $600K in annual sales revenues and include only 2-3 competitors; consolidation among such

[55] For further discussion, see Hemphill and Sampat [2012].
[56] For further discussion, see Berndt, Conti and Murphy [2017].
[57] Woodcock and Wosinska [2015] and Stomberg [2016].
[58] See Federal Trade Commission [2017].

small firms could likely involve transactions less than $80 million, failing to trigger the Hart-Scott-Rodino threshold in spite of generating potential adverse impacts in small but already concentrated markets, resulting in near-monopolies of generic drug markets with minimal if any public scrutiny. Over time such activity could substantially increase concentration of many (or even most) established generic drugs into a very small number of competitors.

Recent Congressional deliberations have raised the issue of whether the FDA should be required to provide expedited review of ANDA applications whenever the generic molecule market has very little competition, defined as three or fewer manufacturers.[59] Our finding that the median number of competitors in a generic molecule market is two and that over 50 percent of generic molecules are supplied by two or fewer one manufacturer suggests that the FDA would likely find this mandate to result in it being required to grant expedited review status to a very large share of ANDA submissions. This raises the issue of whether the anticipated fees collected by generic manufacturers to fund GDUFA's reauthorization will be adequate to meet the potential FDA workload induced by this new review mandate. More fundamentally, U.S. federal policy has only limited experience and modest success in introducing more competition between potential suppliers once the structure of product markets has evolved to become a monopoly, duopoly or limited oligopoly. Those experiences have primarily involved the Department of Justice and the Federal Trade Commission or state-level attorneys general.[60] There is little precedent for using tools at the disposal of the FDA to increase generic competition.

Our results are preliminary and their limitations suggest potentially fruitful areas for future research. Regarding data integrity, there appear to be a fairly substantial number of mnf x molecule x quarter triads with suspiciously low revenues; approximately 10% of mnf x mlist x quarter triads have less than $1,000 dollars in revenue. QuintilesIMS staff informed us there are no minimal cutoff thresholds governing whether to report non-zero sales. Use of alternative arbitrary cutoff values in sales revenue or unit volumes could establish robustness of our findings. Rather than the number of firms that is exiting or entering, another possible metric is

[59] Prescription Drug and Health Improvement Act of 2017: Senator Al Franken. (Accessed on April 19, 2017 at https://www.franken.senate.gov/files/documents/170209PrescriptionDrugandHealthImprovementActof2017OnePager.pdf).

[60] For discussion of the use of U.S. antitrust policy to promote competition across economic sectors, see Scherer and Ross [1990], chapters 9 through 17, and Carlton and Perloff [2005], chapters 16 through 20.

the percent of the market that is exiting or entering, since this alternative would weight differentially the significance of small, possibly falsely, recorded data generating spurious entry and exit. Previous industrial economics studies have reported the sales contribution of new firms in the first year in which they are observed and the sales contribution of exiting firms in the last year in which they were observed to the product market.[61] Based on this measure, one could define average size of entering firm relative to incumbents and the average size of exiting firms relative to non-exiting firms and correlate this with price levels and trends over time.

Another potentially fruitful area of research involves further categorizing manufacturer "type" by identifying the annual revenue, country of incorporation, year of incorporation, organizational structure (standalone corporation or subsidiary of another firm, publicly traded or privately held) and the existence and timing of 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. These categorizations could be cross-checked using a web search of all listed manufacturers, trade press and financial services reports (including annual Parexel industry reports), with the presence, date and type of consolidation being noted for each firm. This could provide information on the roles of consolidations and merger and acquisitions on measures of concentration, and ultimately on price levels, price changes and revenues.

Finally, future research might explore use of semi-structural and structural models to relate cross-sectional and dynamic market structure to observed pricing and revenue trends among generic drugs under conditions of imperfect competition.[62] To circumvent issues of endogeneity, one could limit the sample to triopolies, and examine the price and aggregate output effects of exits that result in a duopoly, or entrants that result in a four-firm market.

[62] See Dunne, Klimek, Roberts, Xu [2009], Pesendorfer and Schmidt-Dengler [2003], Bajari, Benkard, and Levin [2007], Pakes, Ostrovsky and Berry [2007], and Aguirregabiria and Mira [2007].

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Figures and Tables

Table 1: Descriptive Statistics of Biopharmaceutical Manufacturers and Molecule Markets by Year

Year	Count of Molecules	Count of Mnf	Count of Corp	Annual Revenue (Mil)	Brand Revenue Share (%)	Generic Revenue Share (%)	Oral Revenue Share (%)	Injectable Revenue Share (%)	Other Revenue Share (%)
2004	1716	517	408	295249	83	17	67	23	10
2005	1797	545	437	296272	82	18	66	24	10
2006	1854	555	428	314382	80	20	64	25	10
2007	1895	565	442	317832	80	20	63	26	11
2008	1960	562	437	317622	79	21	62	27	11
2009	2063	572	449	332008	78	22	61	27	12
2010	2106	583	459	345717	76	24	59	28	12
2011	2147	589	463	351710	74	26	58	29	13
2012	2131	609	478	334160	72	28	54	32	14
2013	2195	621	497	343403	71	29	51	34	15
2014	2225	633	509	385600	72	28	52	34	14
2015	2245	652	521	428482	73	27	51	36	13
2016	2158	651	526	446491	74	26	49	38	13

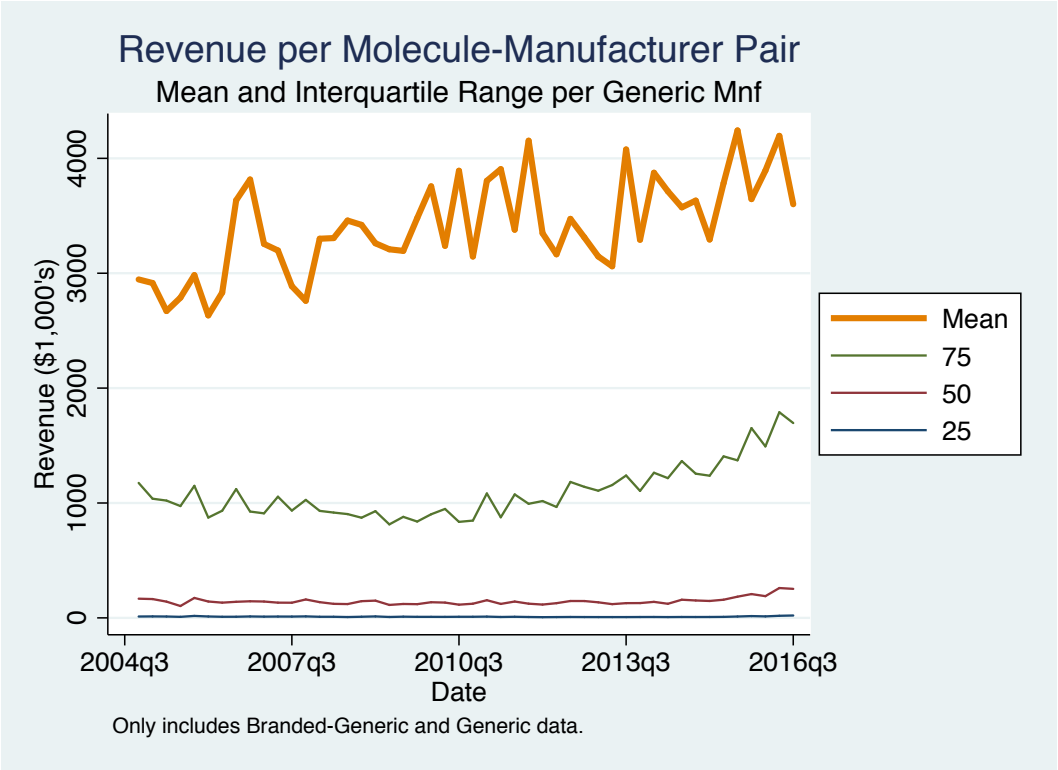
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Annual revenue data is for brands plus generics, deflated by the Gross Domestic Product implicit deflator (2016Q1 = 1.000). Part-year data for 2004 and 2016 annualized by linear extrapolation.

Table 2: Descriptive Statistics of Biopharmaceutical Molecule Markets by Therapeutic Category

ATC1	Count of Molecules	Count of Mnf	Count of Corp	Avg. Annual Rev (Mil)	Brand Rev Share (%)	Generic Rev Share (%)	Oral Rev Share (%)	Injectable Rev Share (%)	Other Rev Share (%)
A	611	369	318	44472	81	19	63	36	1
B	178	184	150	20463	82	18	33	66	1
C	232	260	205	39456	74	26	94	5	1
D	260	208	180	7442	31	69	13	0	87
G	164	208	171	17911	57	43	70	7	23
H	44	131	107	6478	53	47	45	55	1
J	258	235	179	38863	74	26	62	37	1
K	34	25	28	363	4	96	0	99	1
L	206	152	114	42525	92	8	28	72	0
M	240	330	267	39914	73	27	42	48	9
N	192	263	202	53061	76	24	95	3	2
R	315	283	238	26107	80	20	24	3	73
S	160	130	109	7310	60	40	1	1	98
T	57	43	40	1976	89	11	3	92	5
V	565	121	134	1650	82	18	87	8	5

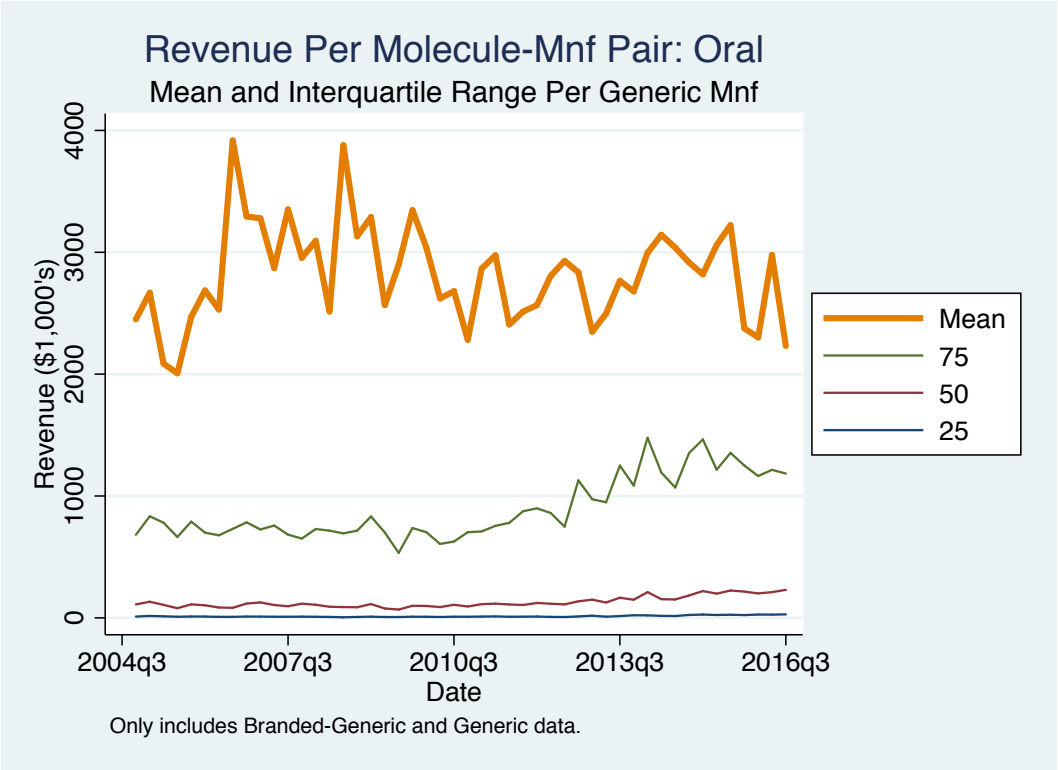
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Annual revenue data is for brands plus generics, deflated by the Gross Domestic Product implicit deflator (2016Q1 = 1.000). Part-year data for 2004 and 2016 annualized by linear extrapolation. ATC1 is a QuintilesIMS slightly modified and aggregated version of the World Health Organization's 244 four-digit anatomic therapeutic classification scheme. See text for legend of ATC1 codes.

Figure 1: Mean, Median, and Interquartile Range of Quarterly Revenue per Generic Molecule-Dosage Form-Manufacturer Sold in the U.S. by Quarter-Year



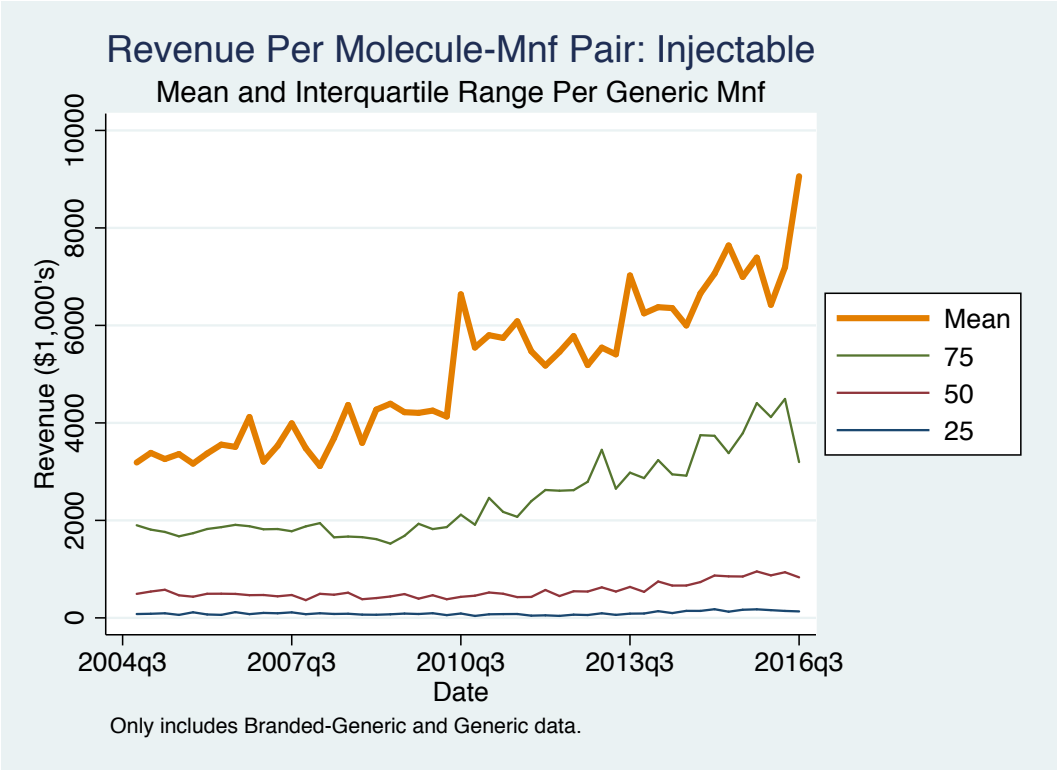
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Revenues are deflated by the Gross Domestic Product implicit deflator (2016Q1 = 1.000).

Figure 2: Mean, Median, and Interquartile Range of Quarterly Revenue per Generic Molecule-Dosage Form-Manufacturer Sold in the U.S by Quarter-Year, Oral Formulated Drugs Only



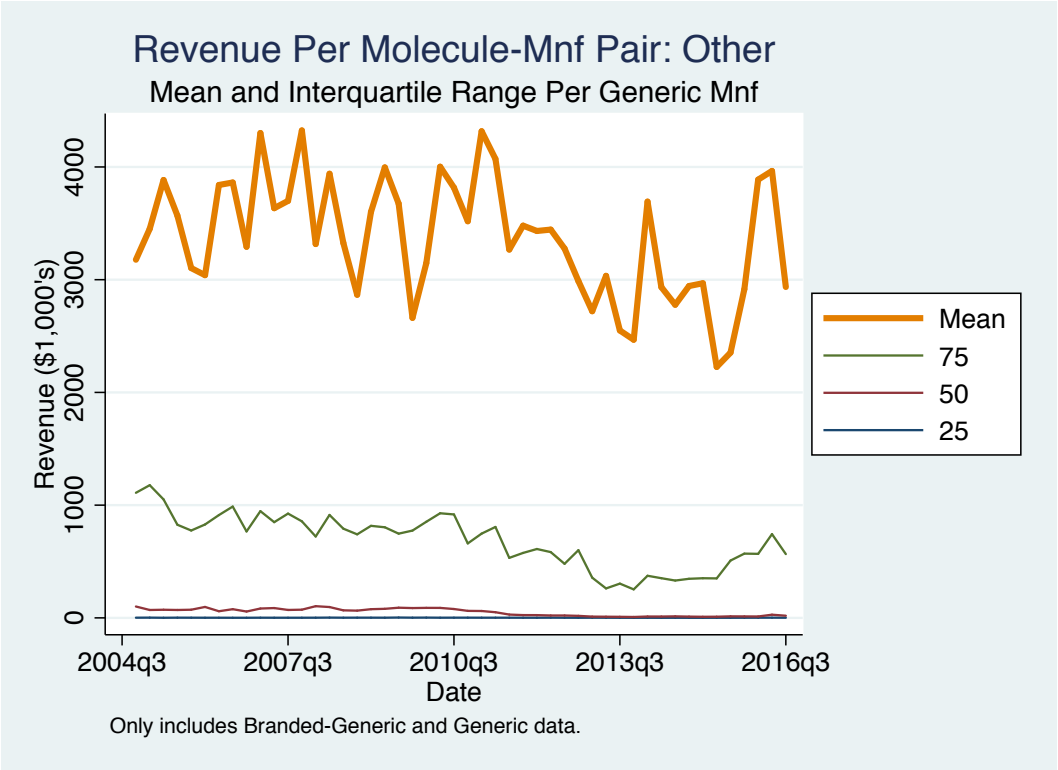
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Revenues are deflated by the Gross Domestic Product implicit deflator (2016Q1 = 1.000).

Figure 3: Mean, Median, and Interquartile Range of Quarterly Revenue per Generic Molecule-Dosage Form-Manufacturer Sold in the U.S by Quarter-Year, Injected or Infused Formulated Drugs Only



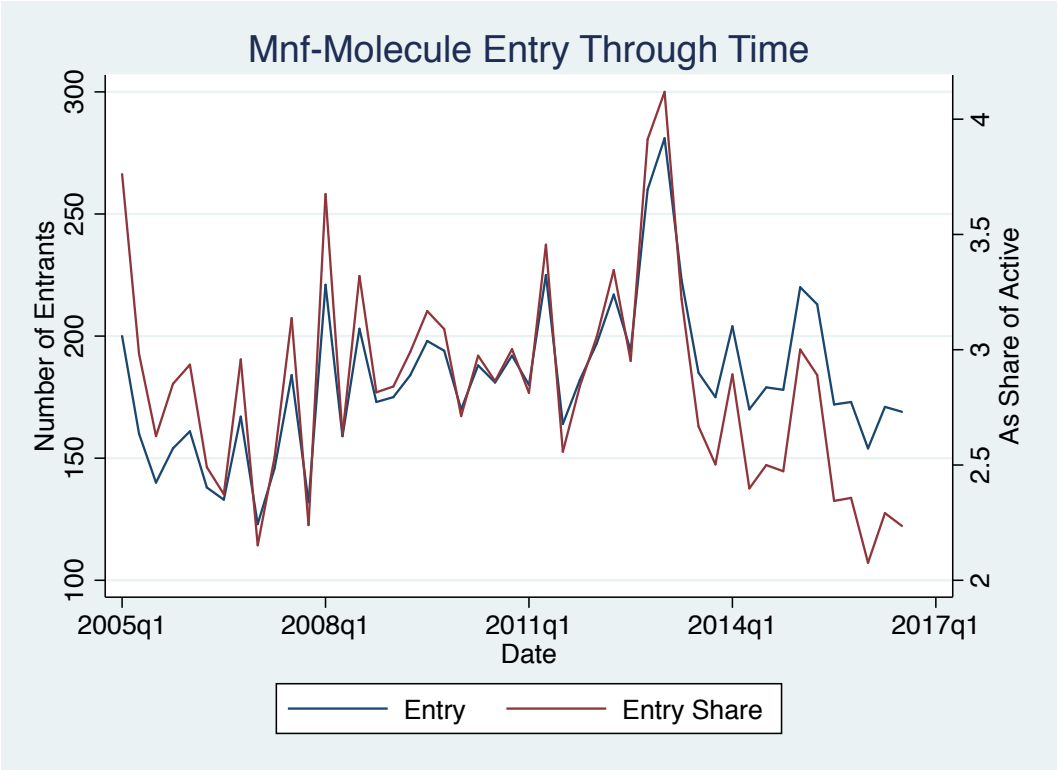
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Revenues are deflated by the Gross Domestic Product implicit deflator (2016Q1 = 1.000).

Figure 4: Mean, Median, and Interquartile Range of Quarterly Revenue per Generic Molecule-Dosage Form-Manufacturer Sold in the U.S by Quarter-Year, "Other" Formulated Drugs Only



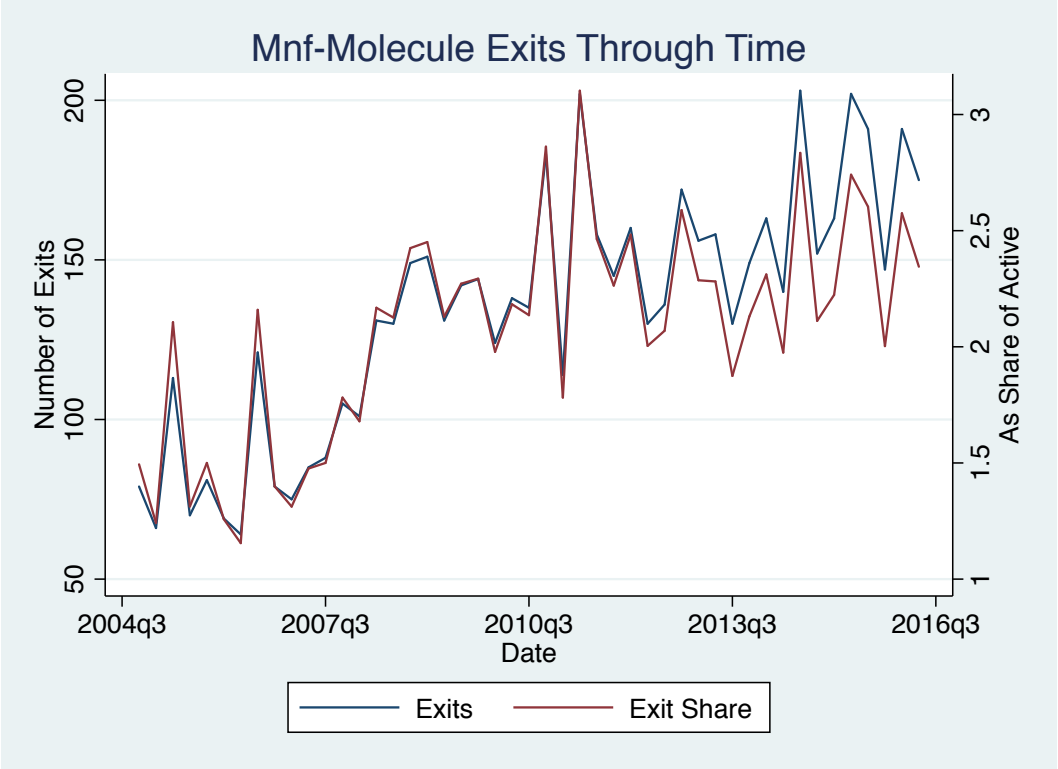
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Revenues are deflated by the Gross Domestic Product implicit deflator (2016Q1 = 1.000).

Figure 5: Generic Manufacturer-Molecule-Dosage Form Entry Patterns between 2004 and 2016 by Quarter-Year



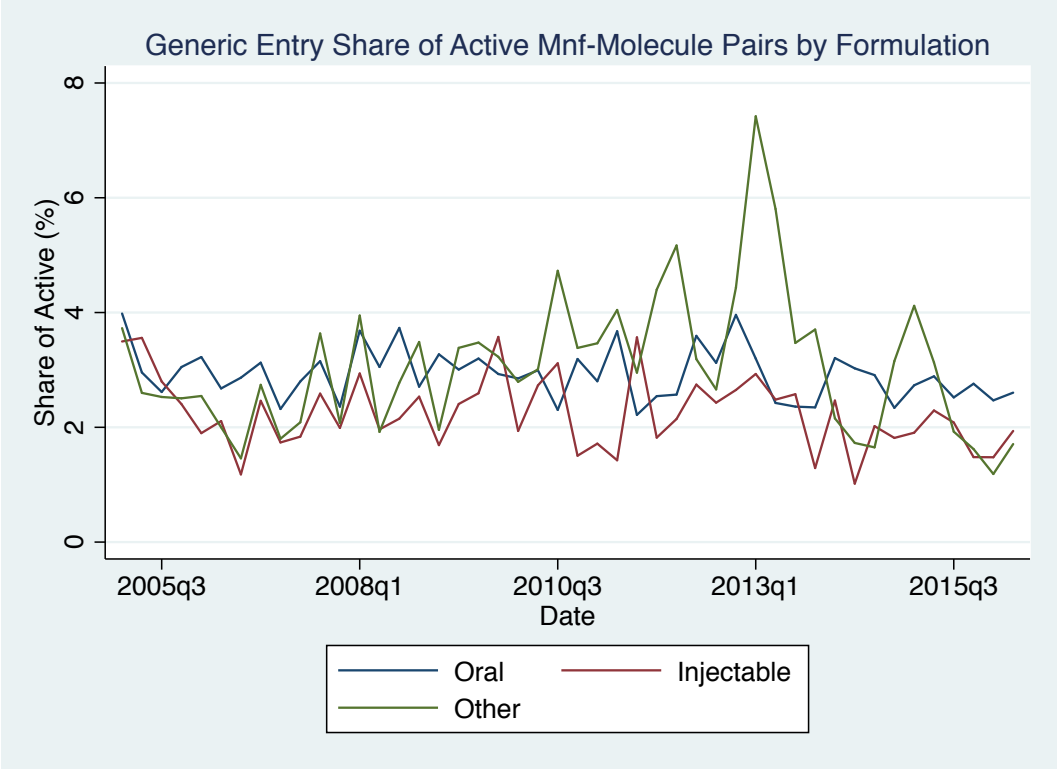
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. On right vertical axis, share = 2 implies a 2.0% share, 2.5 a 2.5% share, etc. Entrant defined as manufacturers of molecules observed immediately following two quarters of zero unit volume and dollar sales, followed by at least two quarters of positive unit volume and sales data of the molecule.

Figure 6: Generic Manufacturer-Molecule-Dosage Form Exit Patterns between 2004 and 2016 by Quarter-Year



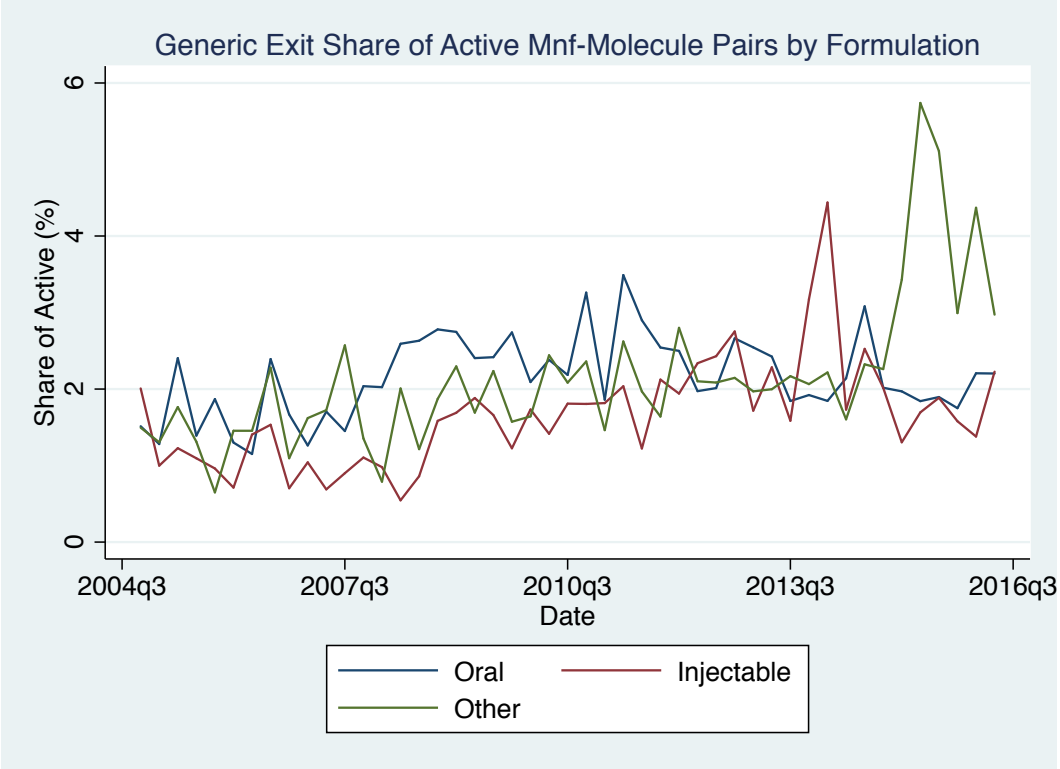
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. On right vertical axis, share = 2 implies a 2.0% share, 2.5 a 2.5% share, etc. Exit defined as manufacturers of molecules that are observed to have at least two quarters of zero unit volume and dollar sales, following at least two quarters of positive unit volume and dollar sales.

Figure 7: Generic Entry Share Disaggregated by Molecule Dosage Form-Quarter-Year



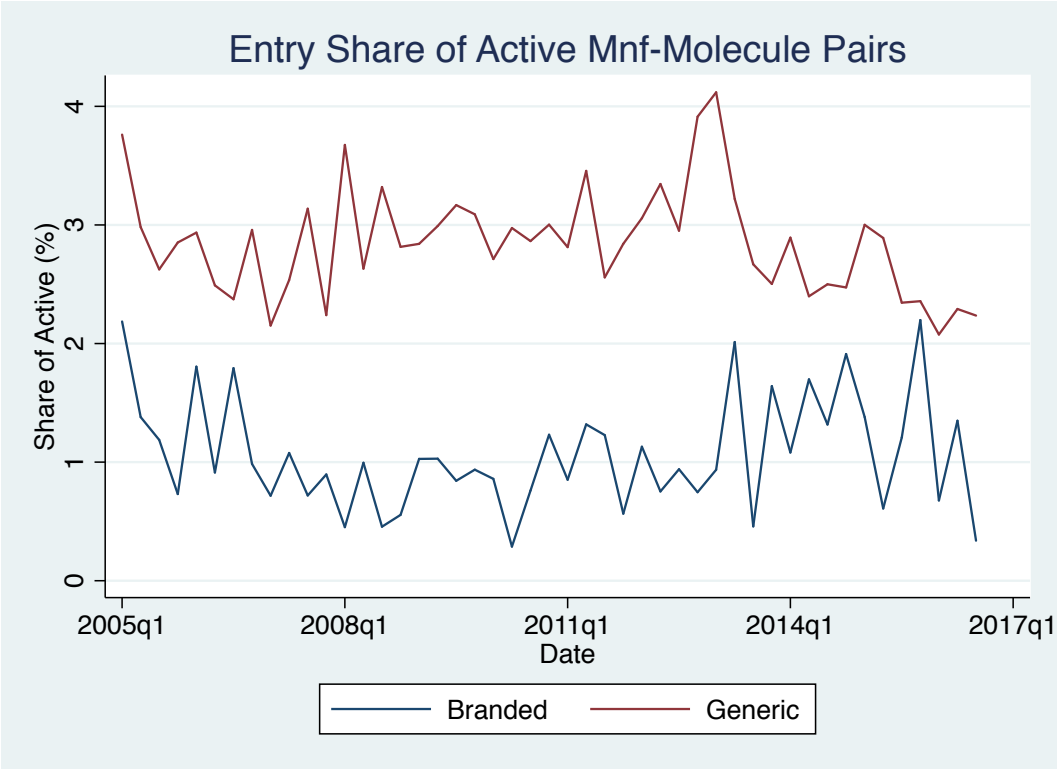
Source: Authors calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Entrant defined as manufacturers of molecules observed immediately following two quarters of zero unit volume and dollar sales, followed by at least two quarters of positive unit volume and sales data of the molecule.

Figure 8: Generic Exit Share Disaggregated by Molecule Dosage Form-Quarter-Year



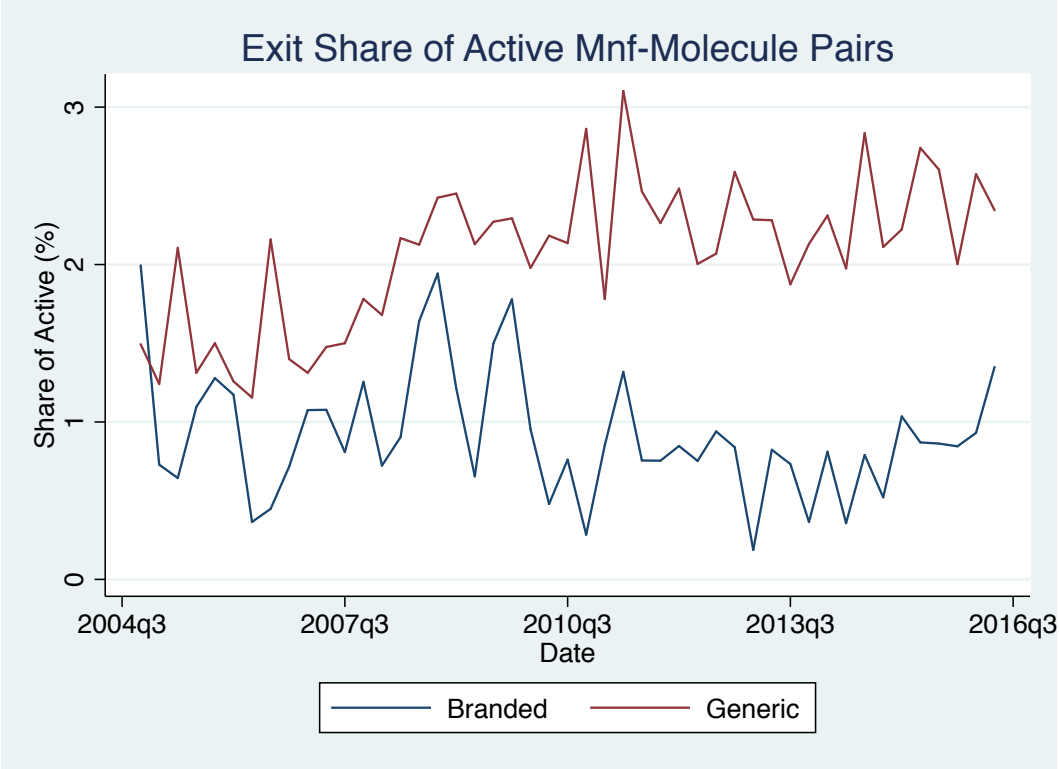
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Exit defined as manufacturers of molecules that are observed to have at least two quarters of zero unit volume and dollar sales, following at least two quarters of positive unit volume and dollar sales.

Figure 9: Manufacturer Entry Share Over Time between Drugs by Patent Status



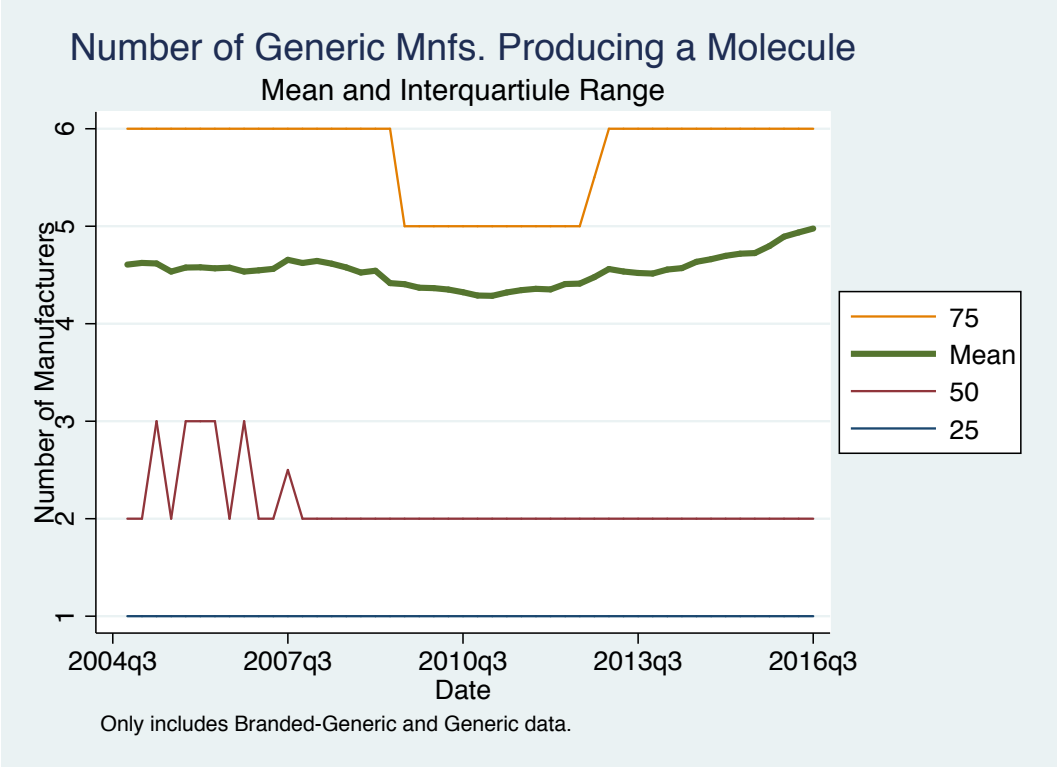
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics include branded generics. On left vertical axis, share 2 refers to a 2.0% share, share 3 refers to a 3.0% share, etc. See Figure 5 legend for definition of entrant.

Figure 10: Manufacturer Exit Share Over Time between Drugs by Patent Status



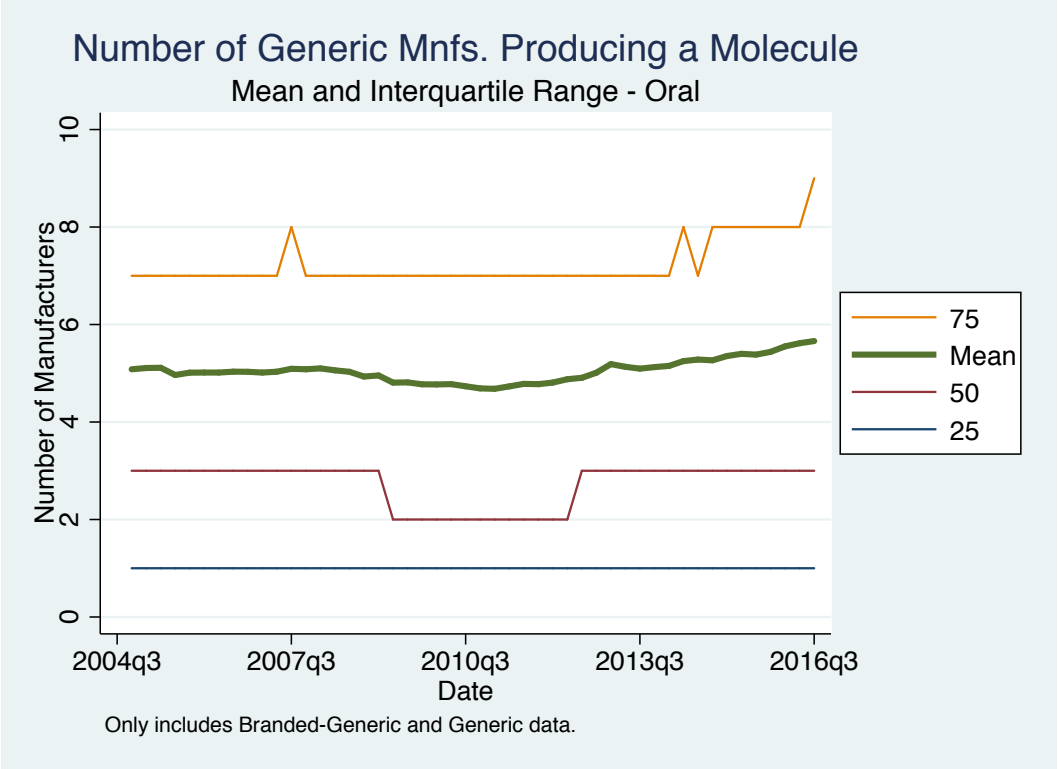
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics include branded generics. On left vertical axis, share 2 refers to a 2.0% share, share 3 refers to a 3.0% share, etc. See Figure 6 legend for definition of exiting molecule product.

Figure 11: Mean and Interquartile Range of Manufacturer Counts per Generic Molecule Dosage Form by Quarter-Year



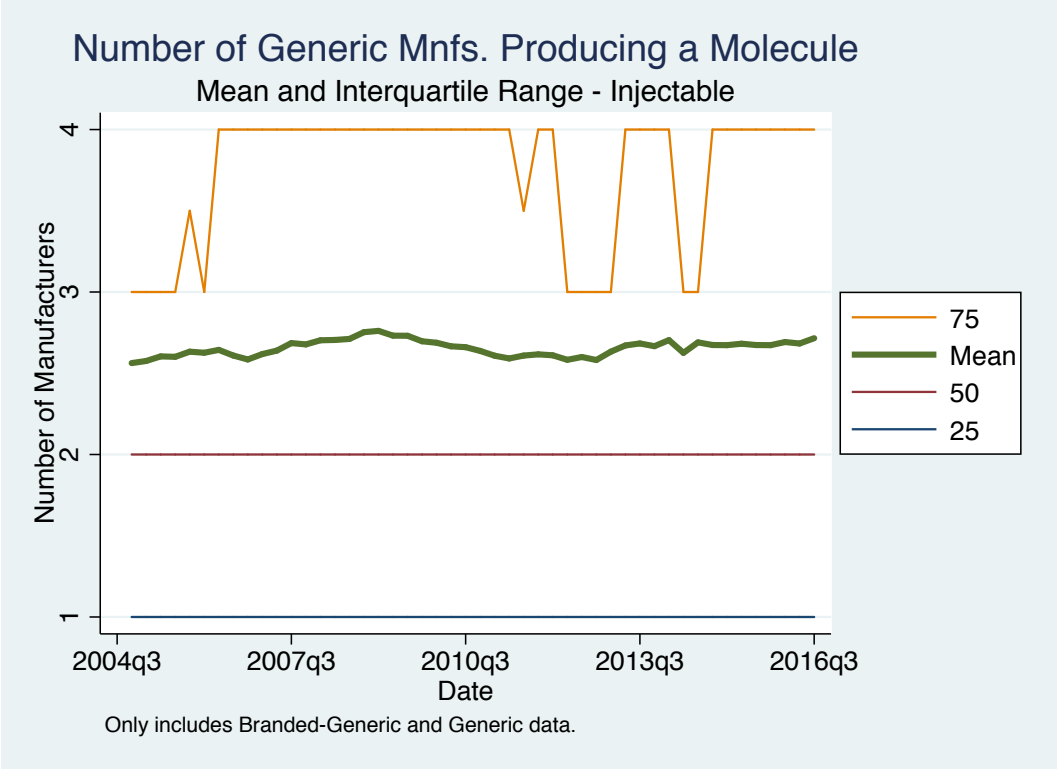
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 12: Manufacturer per Molecule Counts among Oral Generic Drugs by Quarter-Year



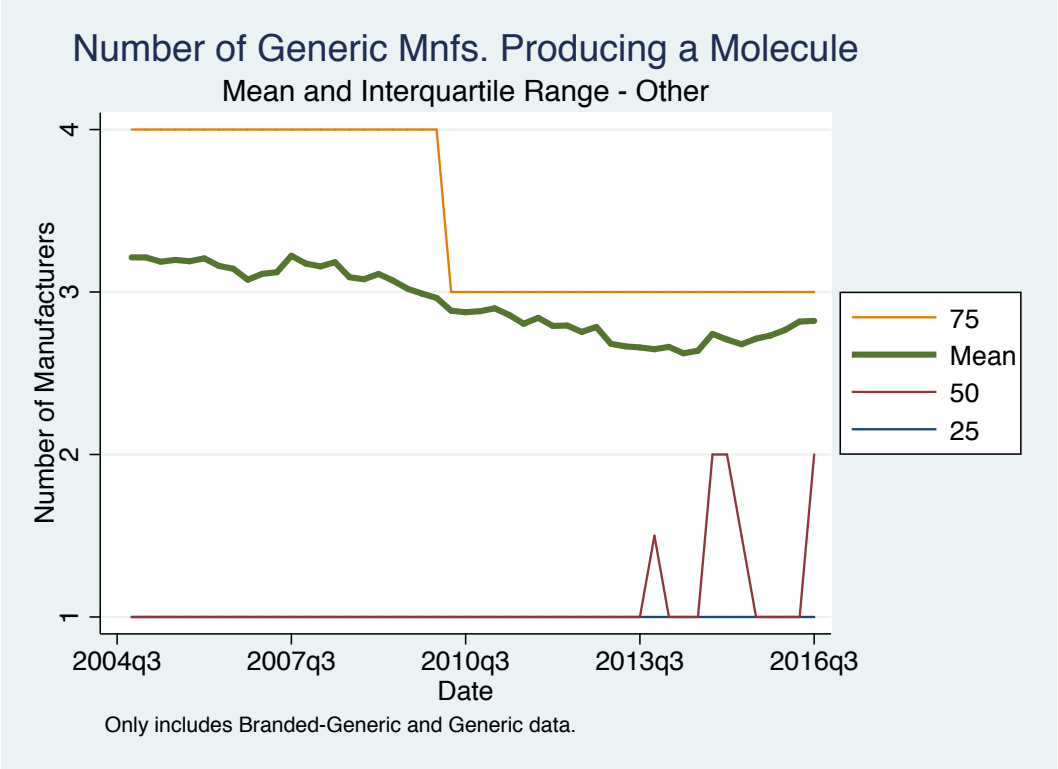
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 13: Manufacturer per Molecule Counts among Infused or Injected Generic Drugs by Quarter-Year



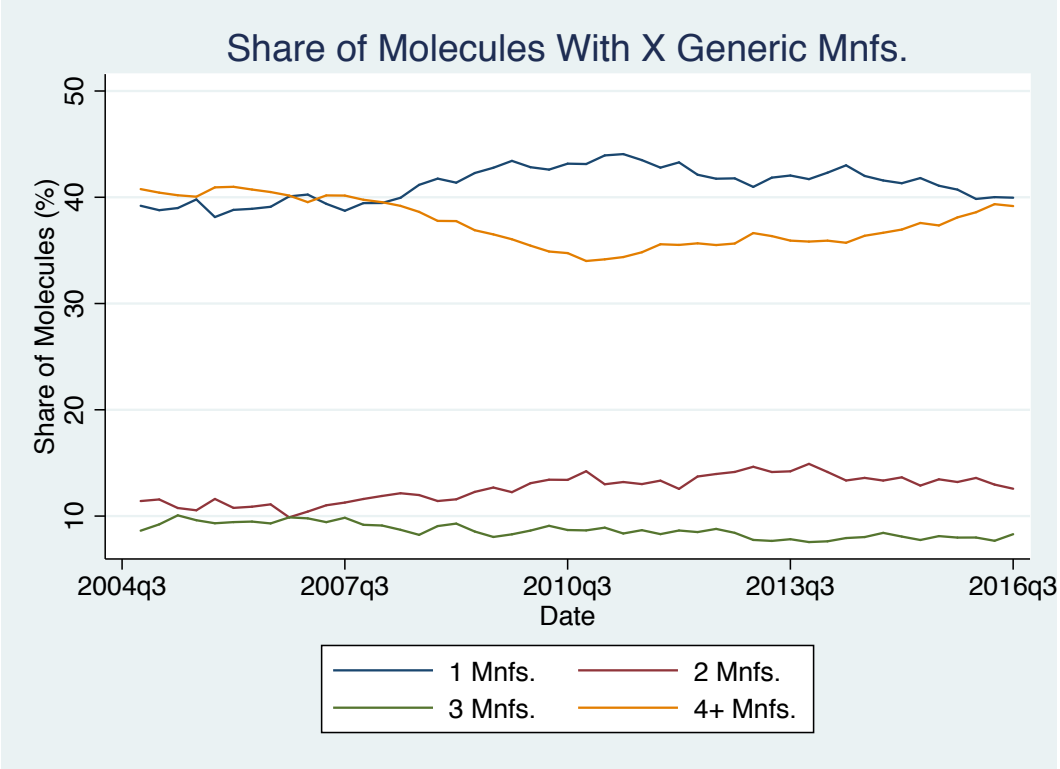
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 14: Manufacturer per Molecule Counts among Other Dosage Form Generic Drugs by Quarter-Year



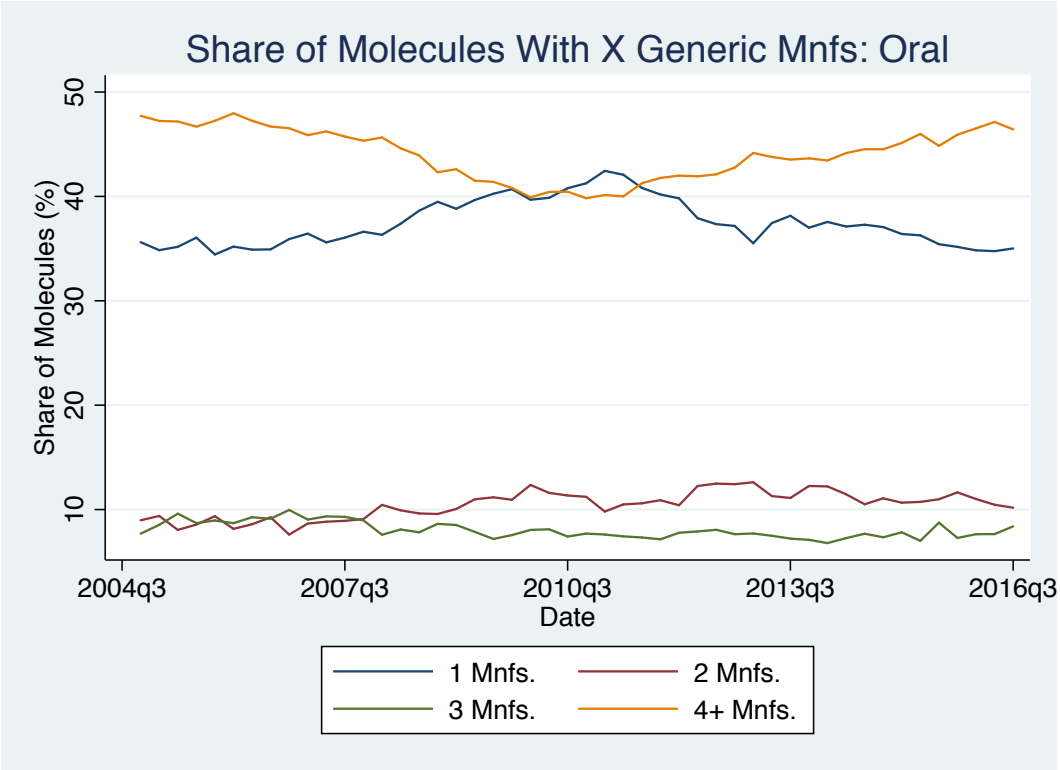
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 15: Share of Molecules by Number of Generic Manufacturers



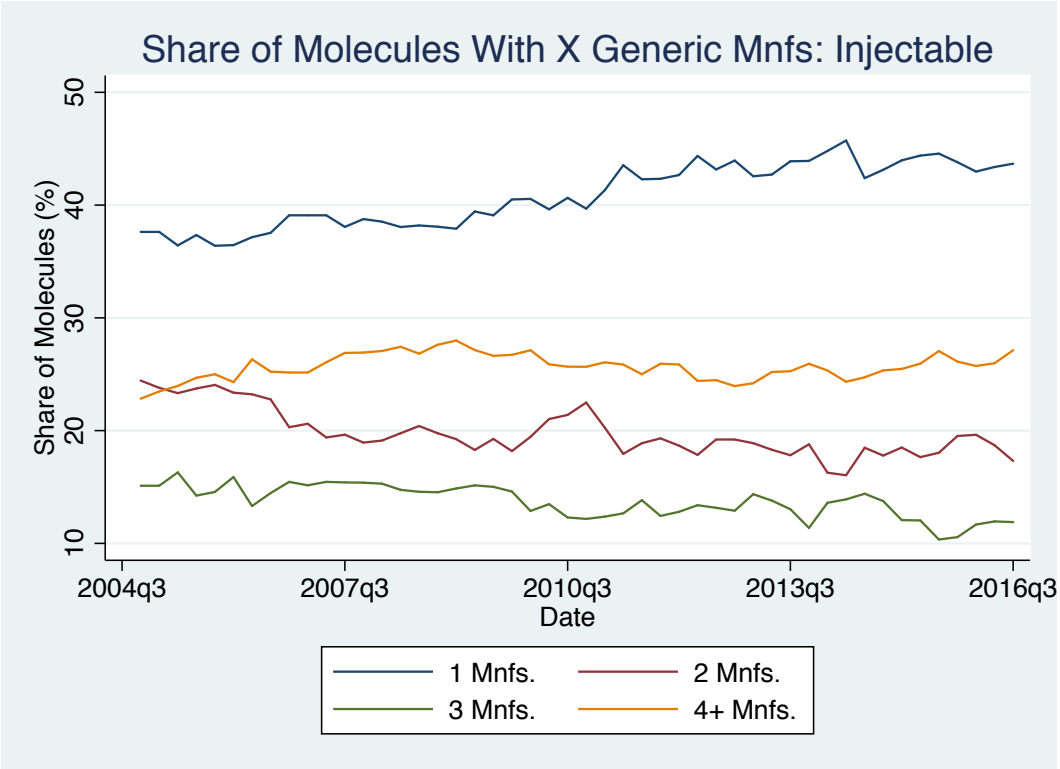
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 16: Share of Oral Molecule Formulations by Number Generic Manufacturers



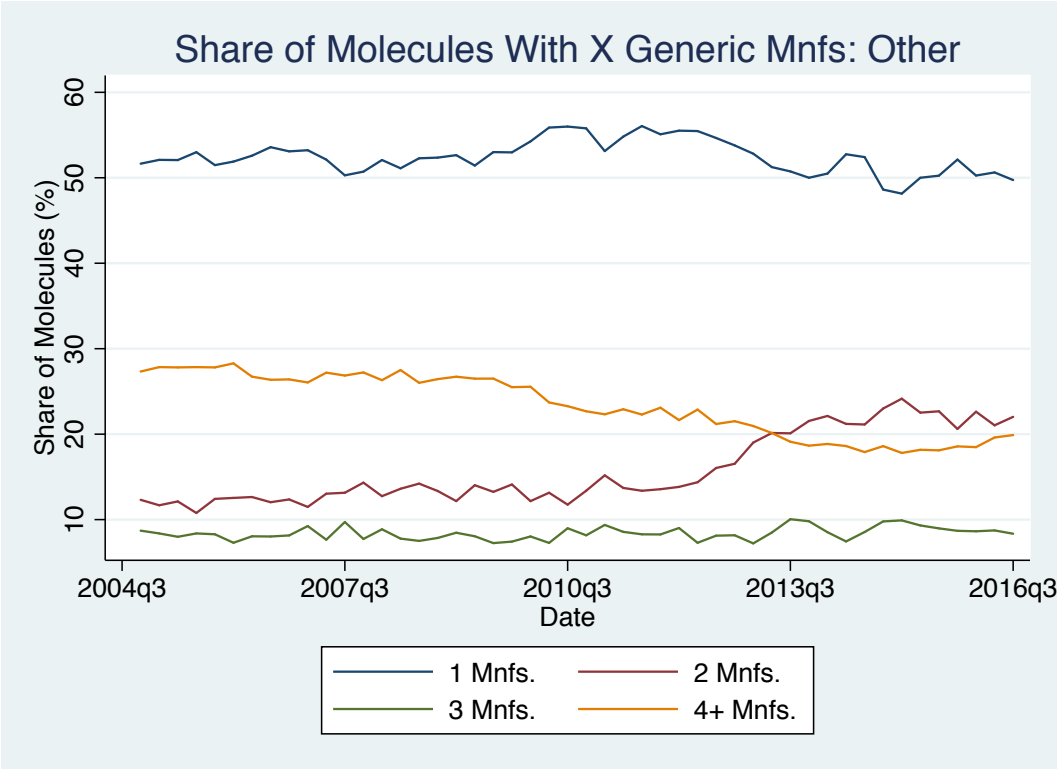
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 17: Share of Injectable Molecule Formulations by Number Generic Manufacturers



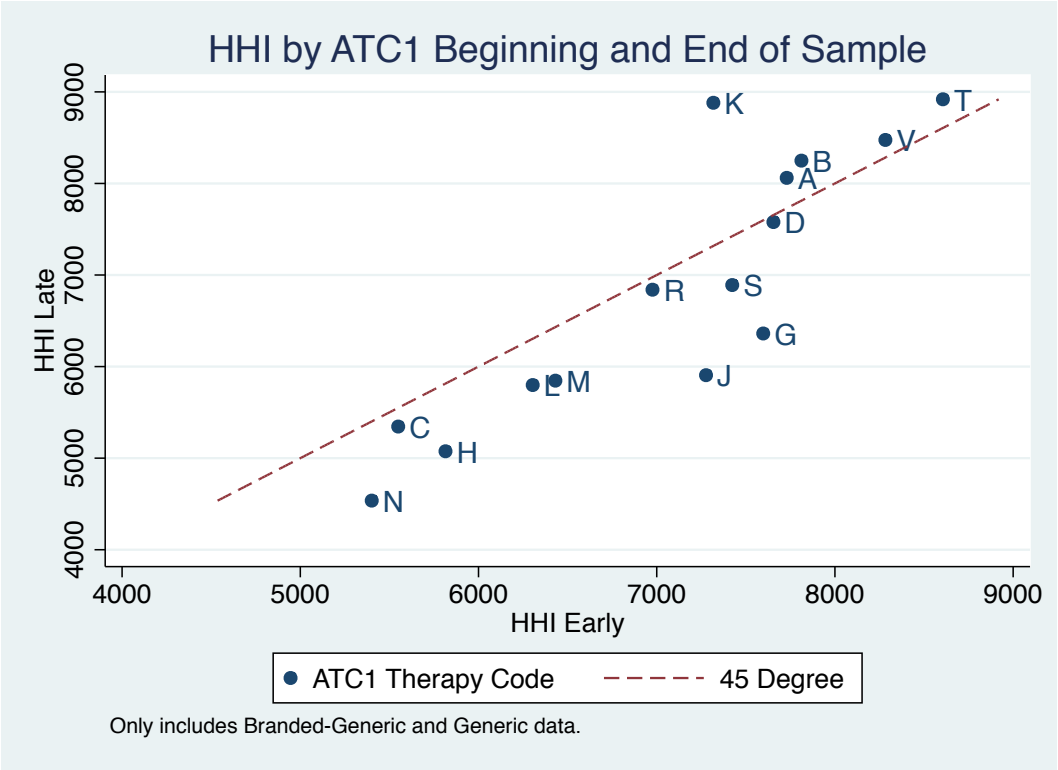
Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 18: Share of Other Molecule Formulations by Number Generic Manufacturers



Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Number of manufacturers of molecule defined as: For each molecule-dosage form quarterly observation, the number of unique manufacturers supplying positive unit volumes and reporting positive dollar sales revenue in that quarter are counted.

Figure 19: Average Manufacturer Concentration among Only Generic Drugs by Therapeutic Class in Q2 2005 and Q1 2016



Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Herfindahl-Hirschman Index (HHI) based on shares between 0 and 100. Aggregate HHI by ATC1 therapeutic class (see text for legend), averaged over all molecules in that therapeutic class. Points above 45 degree line are classes that have become more concentrated over time, based on the average HHI in the class, while points below the 45 degree line have become less concentrated. A market with an HHI of 10,000 may still have competition from a branded product.

Table 3: Regression Results on Generic Exit Share

	(1) Exit Share	(2) Exit Share	(3) Exit Share	(4) Exit Share	(5) Exit Share
1_PreMMA	0.000	0.000			
2_MMA	0.339***	0.354***			
3_ACA	0.816***	0.949***			
4_GDUFA	0.754***	0.897***			
ALL OTHERS		0.000	0.000	0.000	0.000
INJECTABLE		0.200	0.208	0.304*	0.339
ORAL		0.500***	0.502***	0.596***	0.891***
A		0.000	0.000	0.000	0.000
B		-0.483***	-0.490***	-0.682**	-0.495***
C		-0.398***	-0.404***	-0.197	-0.402***
D		0.106	0.105	0.081	0.109
G		-0.596***	-0.601***	-0.083	-0.602***
H		-0.319*	-0.320*	-0.106	-0.325*
J		-0.362***	-0.368***	0.033	-0.371***
K		-0.461	-0.471	-0.984*	-0.483
L		-0.604***	-0.613***	-0.341	-0.616***
M		-0.041	-0.043	0.343	-0.051
N		-0.599***	-0.610***	-0.223	-0.606***
R		2.345***	2.360***	1.492***	2.331***
S		0.233	0.239	0.795**	0.249
T		-0.127	-0.117	-0.805	-0.113
V		2.677***	2.642***	-1.174**	2.577***
Time Trend			0.025***		
A × Time Trend				0.026***	
B × Time Trend				0.033***	
C × Time Trend				0.018***	
D × Time Trend				0.030***	
G × Time Trend				0.006	
H × Time Trend				0.017	
J × Time Trend				0.010	
K × Time Trend				0.046*	
L × Time Trend				0.016	
M × Time Trend				0.010*	
N × Time Trend				0.011**	
R × Time Trend				0.071***	
S × Time Trend				0.006	
T × Time Trend				0.056*	
V × Time Trend				0.149***	
ALL OTHERS × Time Trend					0.036***
INJECTABLE × Time Trend					0.031***
ORAL × Time Trend					0.021***
Constant	1.552***	1.035***	1.041***	0.939***	0.771***
Clusters	2273	2273	2273	2273	2273
R-sqr	0.001	0.013	0.013	0.015	0.014
Obs.	77797	77797	77797	77797	77797

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. See legend in Figure 6 for definition of exiting molecule products, and text for definition of regulatory regimes. Ordinary least squares estimates with standard errors clustered at the molecule level. To save on space, standard errors are not reported. Column 1 regresses the molecule-manufacturer exit share on dummies for regulatory regime. Column 2 adds dummies for formulation type and ATC1 therapeutic class. Column 3 adds a single linear time trend. Column 4 deletes simple linear time trend and adds interaction terms between time trend and ATC1 class. Column 5 replaces time trend and ATC1 interaction terms with time trend and formulation interaction terms.

Table 4: Regression Results of Generic Entry Share

	(1) Entry Share	(2) Entry Share	(3) Entry Share	(4) Entry Share	(5) Entry Share
1_PreMMA	0.000	0.000			
2_MMA	-0.251	-0.267			
3_ACA	-0.016	-0.100			
4_GDUFA	-0.431**	-0.650***			
ALL OTHERS		0.000	0.000	0.000	0.000
INJECTABLE		-0.414*	-0.414*	-0.476**	-0.714*
ORAL		0.363*	0.362*	0.304	-0.002
A		0.000	0.000	0.000	0.000
B		0.085	0.083	-0.096	0.085
C		-0.060	-0.064	-0.066	-0.065
D		0.048	0.044	0.246	0.038
G		-0.132	-0.136	-0.977*	-0.137
H		-0.634*	-0.641*	-0.629	-0.637*
J		0.359	0.359	0.920	0.358
K		-0.239	-0.245	-0.581	-0.240
L		0.762*	0.767*	1.017	0.764*
M		-0.217	-0.222	-0.591	-0.217
N		0.332	0.330	0.420	0.326
R		0.046	0.028	0.727	0.048
S		-0.554**	-0.555**	-0.420	-0.566**
T		-1.122***	-1.122***	-0.893	-1.121***
V		4.448***	4.430***	7.344***	4.492***
Time Trend			-0.014***		
A × Time Trend				-0.009	
B × Time Trend				-0.002	
C × Time Trend				-0.009	
D × Time Trend				-0.018*	
G × Time Trend				0.022*	
H × Time Trend				-0.009	
J × Time Trend				-0.030**	
K × Time Trend				0.003	
L × Time Trend				-0.018	
M × Time Trend				0.006	
N × Time Trend				-0.012	
R × Time Trend				-0.042***	
S × Time Trend				-0.016*	
T × Time Trend				-0.018	
V × Time Trend				-0.101***	
ALL OTHERS × Time Trend					-0.025***
INJECTABLE × Time Trend					-0.014*
ORAL × Time Trend					-0.011**
Constant	3.076***	2.811***	2.846***	2.758***	3.127***
Clusters	2276	2276	2276	2276	2276
R-sqr	0.000	0.008	0.007	0.008	0.007
Obs.	78295	78295	78295	78295	78295

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. See legend in Figure 5 for definition of entrant share, and text for definition of regulatory regimes. Ordinary least squares estimates with standard errors clustered at the molecule level. To save on space, standard errors are not reported. Column 1 regresses the molecule-manufacturer entry share on dummies for regulatory regime. Column 2 adds dummies for formulation type and ATC1 therapeutic class. Column 3 adds a single linear time trend. Column 4 deletes simple linear time trend and adds interaction terms between time trend and ATC1 class. Column 5 replaces time trend and ATC1 interaction terms with time trend and formulation interaction terms.

Table 5: Regression Results of Log Inflation-Adjusted Generic Price on Supplier Counts

	(1) Log Price	(2) Log Price	(3) Log Price	(4) Log Price	(5) Log Price	(6) Log Price	(7) Log Price	(8) Log Price	(9) Log Price	(10) Log Price	(11) Log Price	(12) Log Price	(13) Log Price
Log Corp		-0.736***	-0.737***	-0.798***	-0.803***	-0.732***	-0.378***						
Log Mnf								-0.720***	-0.721***	-0.773***	-0.777***	-0.707***	-0.374***
1_PreMMA	0.000	0.000						0.000					
2_MMA	0.101***	0.075***						0.081***					
3_ACA	0.401***	0.331***						0.337***					
4_GDUFA	0.751***	0.719***						0.724***					
A				0.000						0.000			
B				0.989***						0.987***			
C				0.659***						0.660***			
D				0.999***						0.997***			
G				1.877***						1.871***			
H				1.384***						1.374***			
J				2.698***						2.689***			
K				2.576***						2.574***			
L				4.119***						4.100***			
M				1.223***						1.217***			
N				0.575***						0.588***			
R				0.262**						0.251*			
S				-0.707***						-0.688***			
T				3.575***						3.576***			
V				1.016***						1.017***			
Constant	-0.082	0.668***	1.028***	0.133	0.382	-0.281***	0.526***	0.647***	1.012***	0.111	0.700***	0.669***	0.518***
Date FE	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
ATC1 FE	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
ATC2 FE	No	No	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
ATC3 FE	No	No	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes
Molecule FE	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes
Clusters	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281
R-sqr	0.02	0.11	0.11	0.32	0.45	0.54	0.94	0.11	0.12	0.32	0.45	0.54	0.94
Obs.	67416	67416	67416	67416	67416	67416	67416	67416	67416	67416	67416	67416	67416

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Prices adjusted for inflation using GDP deflator with 2016Q1 = 1.000. See legend for Figure 11 for definition of manufacturer count, and text for corporation count and regulatory regimes. Ordinary least squares estimates with standard errors clustered at the molecule level.

Table 6: Regression Results of Log Inflation-Adjusted Generic Price on Log Concentration

	(1) Log Price	(2) Log Price	(3) Log Price	(4) Log Price	(5) Log Price	(6) Log Price	(7) Log Price	(8) Log Price	(9) Log Price	(10) Log Price	(11) Log Price	(12) Log Price	(13) Log Price
Log HHI		0.892***	0.894***	0.920***	0.965***	0.926***	0.843***						
ALL OTHERS × Log HHI								1.589***	1.589***	1.288***	1.256***	1.245***	1.176***
INJECTABLE × Log HHI								0.895***	0.896***	1.006***	0.999***	0.943***	0.961***
ORAL × Log HHI								0.676***	0.678***	0.775***	0.848***	0.808***	0.657***
1_PreMMA	0.000	0.000						0.000					
2_MMA	0.107***	0.122***						0.127***					
3_ACA	0.445***	0.424***						0.424***					
4_GDUFA	0.836***	0.849***						0.839***					
ALL OTHERS		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
INJECTABLE		2.349***	2.351***	1.654***	1.487***	1.082***	1.022***	2.159***	2.162***	1.598***	1.425***	1.007***	0.954***
ORAL		-0.910***	-0.908***	-1.235***	-1.188***	-1.588***	-1.570***	-1.216***	-1.213***	-1.409***	-1.333***	-1.740***	-1.829***
A				0.000						0.000			
B				0.467***						0.462***			
C				0.152						0.109			
D				0.125						0.137			
G				1.549***						1.524***			
H				0.540*						0.501*			
J				1.252***						1.213***			
K				0.313						0.266			
L				2.297***						2.268***			
M				0.505***						0.468***			
N				0.367**						0.304**			
R				0.251*						0.247*			
S				-1.585***						-1.564***			
T				1.825***						1.791***			
V				0.568***						0.508**			
Constant	0.055	0.384***	0.831***	0.746***	0.778***	1.087***	1.240***	0.576***	1.022***	0.866***	0.857***	1.172***	1.367***
Date FE	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
ATC1 FE	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
ATC2 FE	No	No	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
ATC3 FE	No	No	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes
Molecule FE	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes
Clusters	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281	2281
R-sqr	0.02	0.37	0.37	0.45	0.51	0.57	0.86	0.38	0.38	0.46	0.51	0.57	0.86
Obs.	79641	79641	79641	79641	79641	79641	79641	79641	79641	79641	79641	79641	79641

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Source: Authors' calculations based on QuintilesIMS National Sales Perspective database, 2004Q4 - 2016Q3. Generics only, including branded generics but excluding brands. Prices adjusted for inflation using GDP deflator with 2016Q1 = 1.000. See legend for Figure 19 and text for definition of Herfindahl-Hirschman Index (HHI), and text for definition of regulatory regimes. Ordinary least squares estimates with standard errors clustered at the molecule level.