

Challenges in Maintaining Competition in Small Generic Drug Markets II

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Global Opportunities and Challenges in Using Quantitative Methods and Modeling in
Modernizing Generic Drug Development, Regulatory Review and Product Lifecycle
Management

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Background to Empirical Questions

- Generic drug market have commonly been characterized as encompassing a virtuous circle:
 - Following FDA certification of interchangeability, extensive entry and price competition among generic manufacturers facilitated by strong demand growth, has resulted in increasing access to affordable treatments and low spending growth, offsetting spending growth on branded drugs.
- Yet, stakeholders worry this promise is fading:
 - 2009-2017: High-profile shortages among old injectable and some old oral generic drugs.
 - 2012-2013: Increases in the prices of many incumbent generic drugs, increasing overall generic drug spending.
 - 2015-2017: Massive price spikes for selected old drugs that are standard of care.

Is Increasing Manufacturer Concentration Driving These Trends?

- Little is known about actual historical patterns of generic manufacturer entry and exit
 - Impacts on US market outcomes (prices, spending, revenues, access).
- Various studies have examined entry and market outcomes in the first 24-months after initial loss of exclusivity (LOE).

Our Focus: 4 Features of Generic Drug Competition 2004Q4 – 2016Q3

- Entry and exit in product markets – any trends since 2012Q4 implementation of GDUFA I?
- Mean and interquartile distribution of revenues per product – mostly small with a few outliers, or relatively homogeneous?
- Number of manufacturers producing a generic molecule-route of administration product – large or small, any trends between 2004 and 2016? Since 2012 implementation of GDUFA I?
- How much competition?

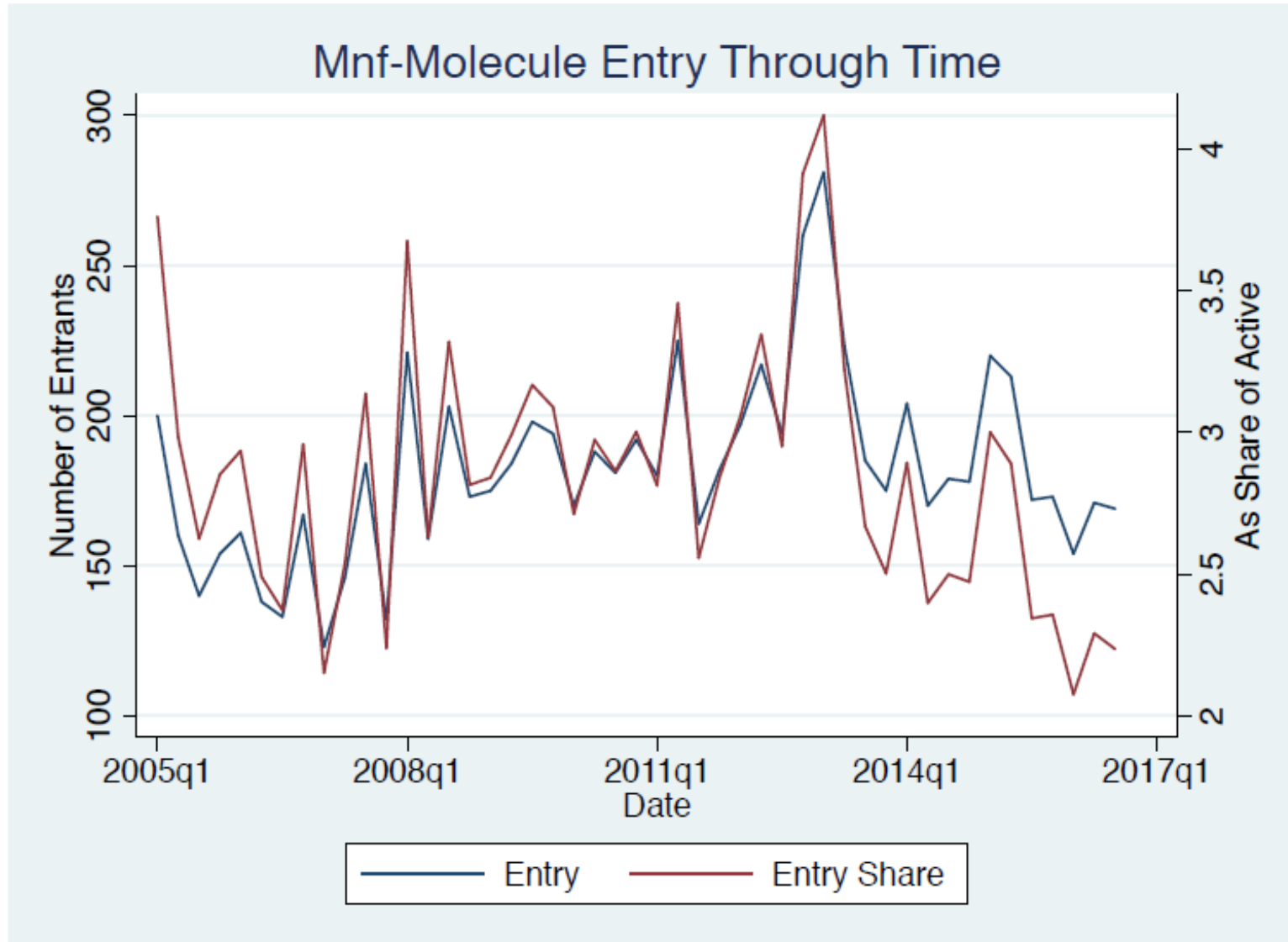
Empirical Methods

- “Product market” will be defined here by molecule-route of administration, e.g., various strengths of oral famotidine (generics and Pepcid) constitute one product market, various strengths of injectable famotidine (generics and Pepcid) constitute another product market, and oral solids ranitidine (brand name Zantac) and famotidine (brand name Pepcid) are in different product markets – in general concordance with FTC/DOJ market definitions. Assumes different strengths of same molecule-route of administration are perfect substitutes (accomplished through tablet splitting or scoring, or multiple tablets/capsules).
- Market structure will be quantified by manufacturer counts, entry and exit in product markets, market shares by suppliers and concentration by Herfindahl-Hirschman Index (HHI).

Data Source: QuintilesIMS National Sales Perspective (NSP)TM

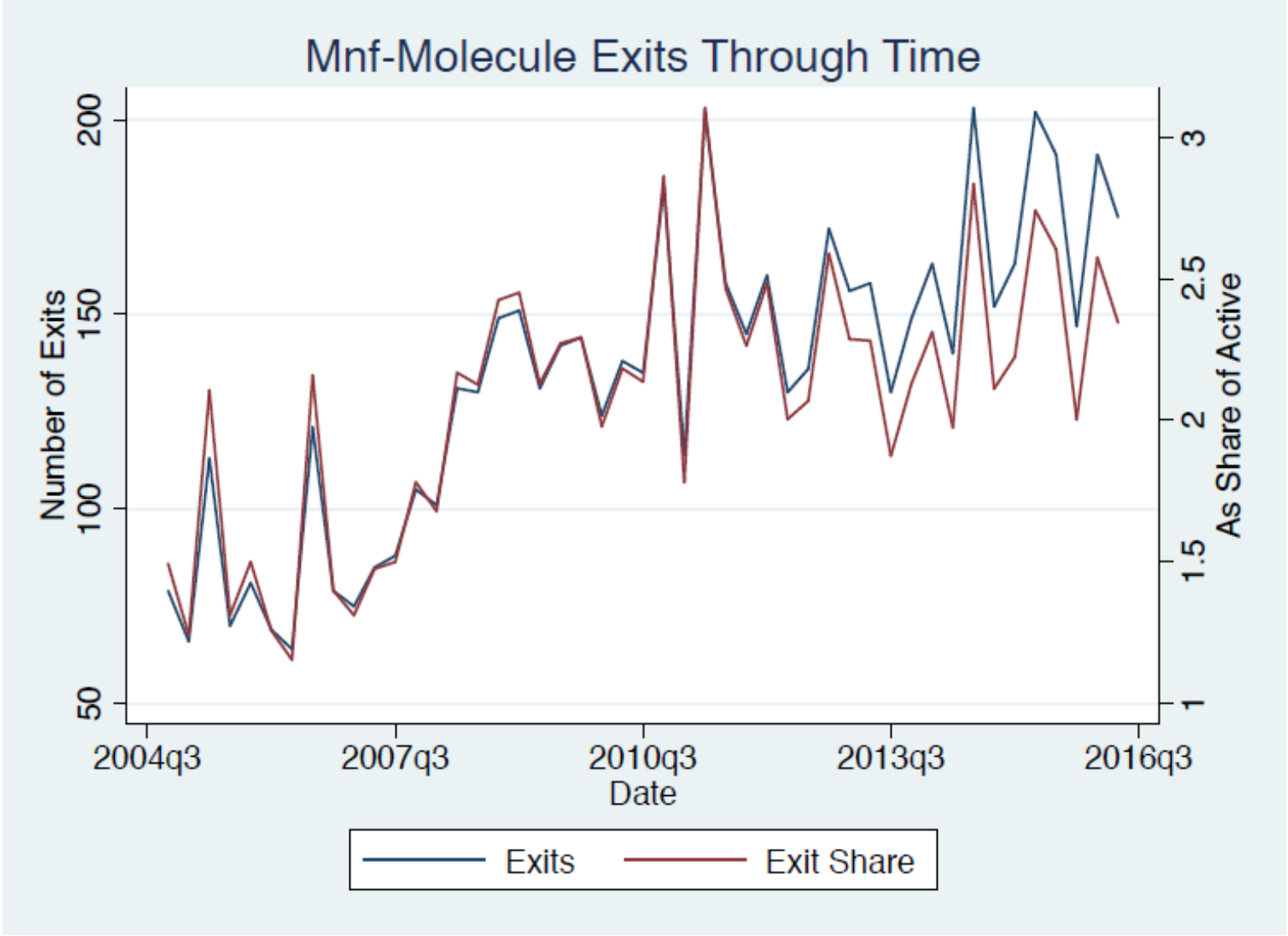
- Quarterly national US data on quantities sold, wholesale dollar sales and suppliers of all prescription drugs taken from QuintilesIMS NSP data asset, 2004Q4 through 2016Q3. Volumes are in standard units.
- NSP data derive from a projected audit covering 100% of the national unit volume and dollar sales in all major classes of trade and distribution channels for U.S. prescription pharmaceuticals. The data derive from an audit of molecule purchases from manufacturers or wholesalers to pharmacies or other distribution outlets, but not retail pharmacy sales to patients.
- NSP provides information on specific chemical and branded names, formulation, dosage and the name of labeler (FDA's terminology for the owner of the NDA or the ANDA in the FDA's Orange Book).

Entry Rates Increasing To 2013, But Falling Back Thereafter To 2005 Levels

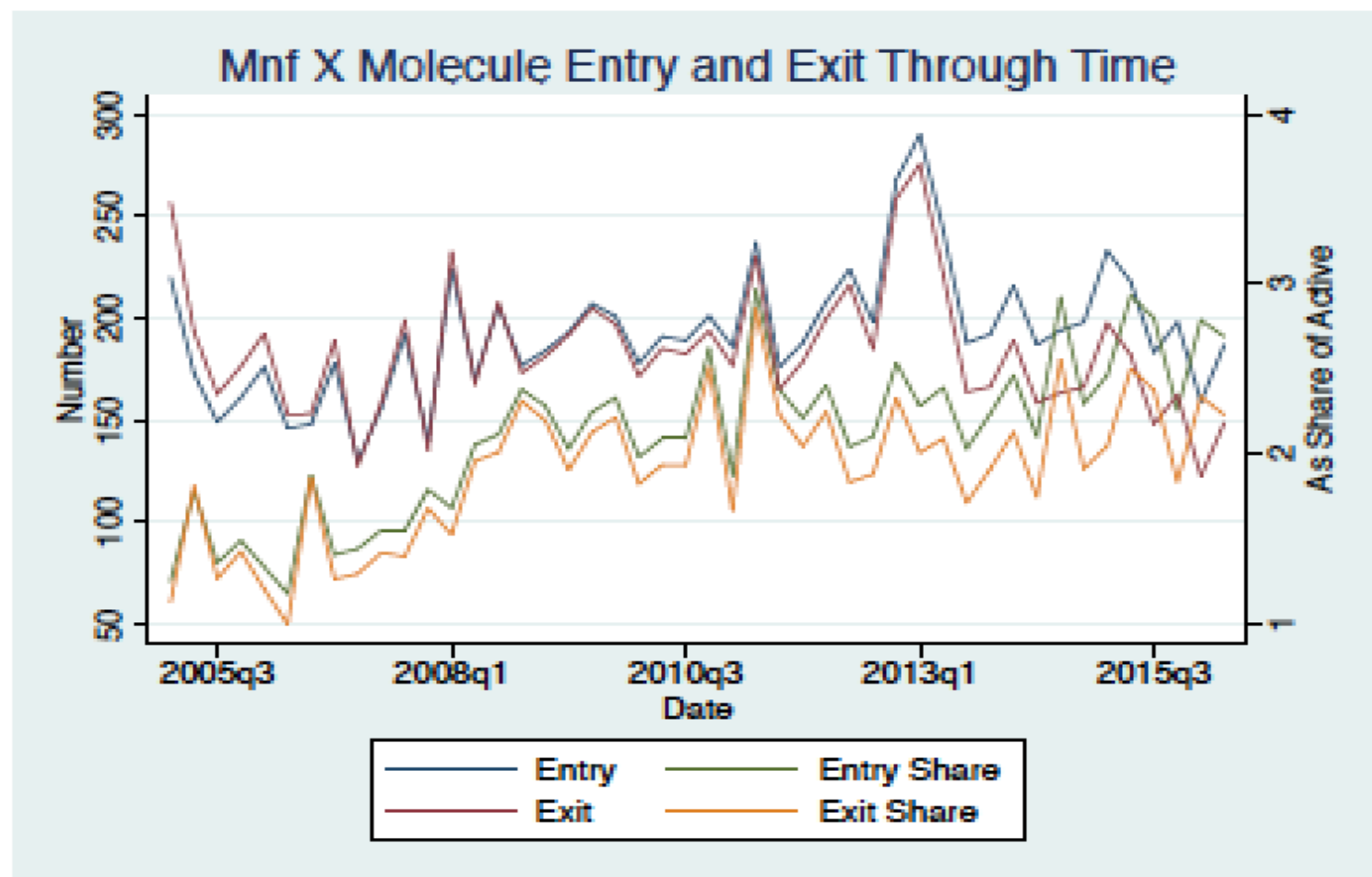




Exit Rates Increasing To 2011, Flat After 2012

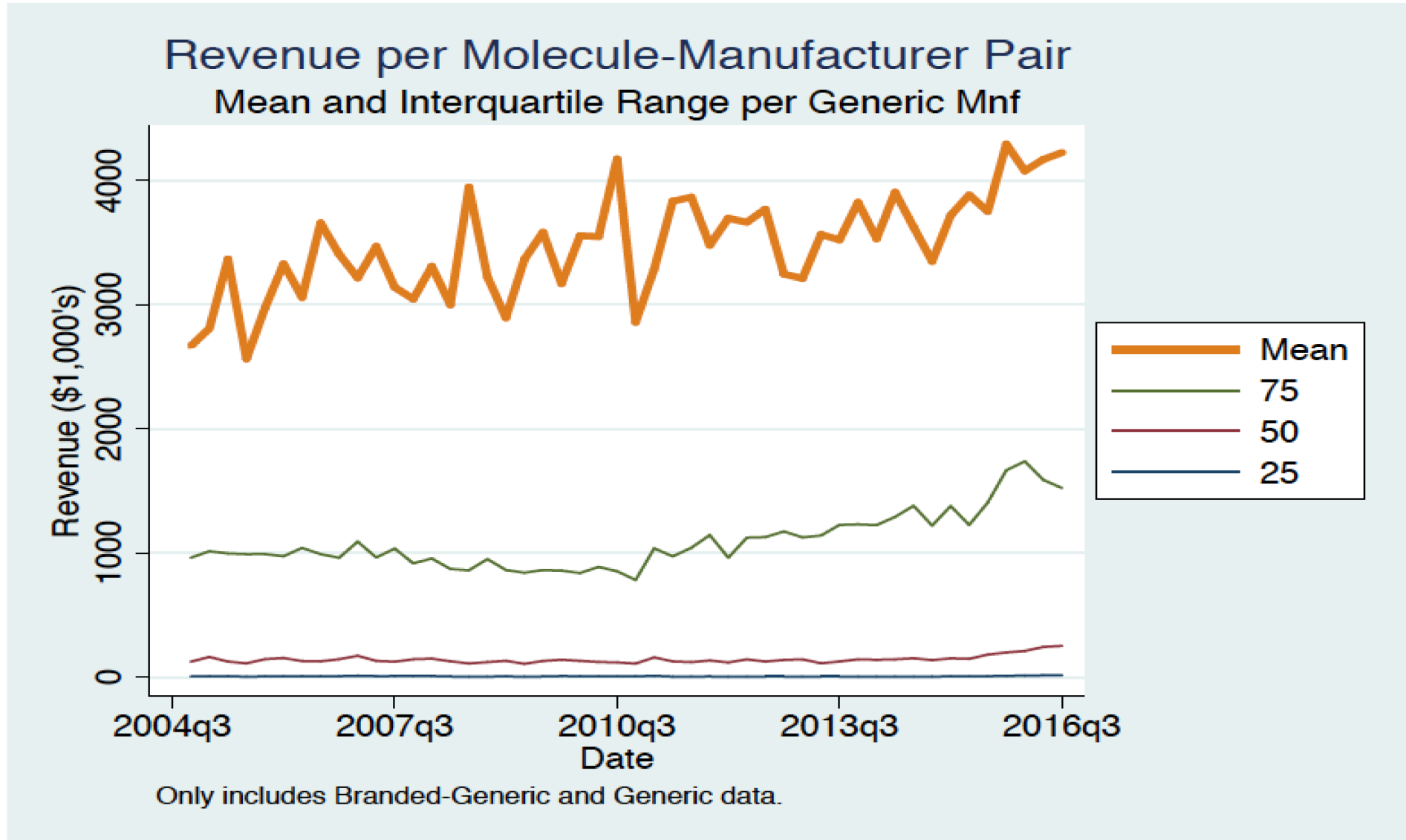


Entry Rates > Exit Rates, Recent Convergence



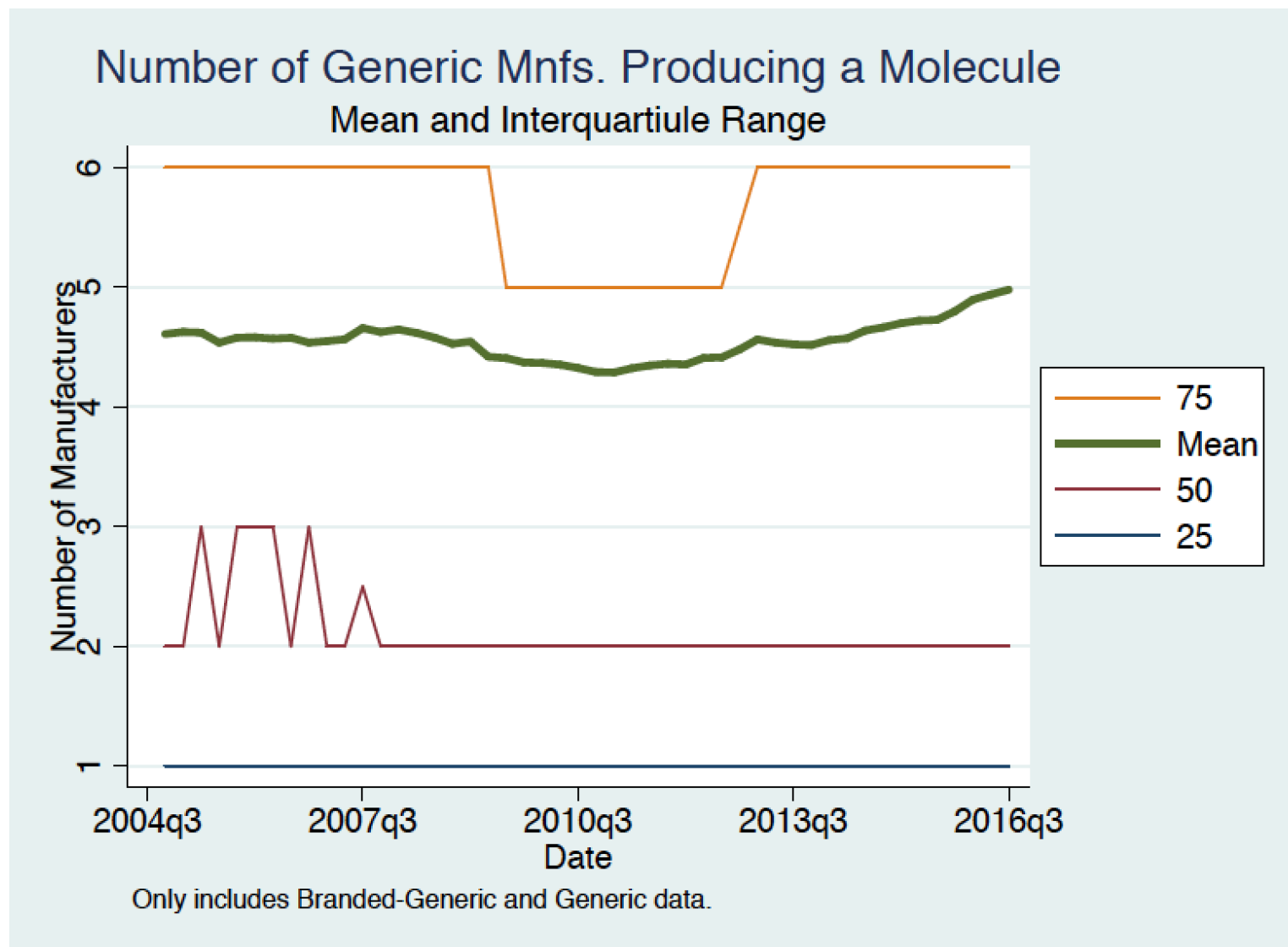
This figure displays the number of new manufacturer by molecule entrants and exits into and from the market across our entire sample. Additionally it provides the share that these entrants / exits represents compared to the stock of the number of currently active manufacturer-molecule pairs.

Median Quarterly Product Revenues Small - \$100k To \$150k - But Mean Even Larger Than 75th Percentile





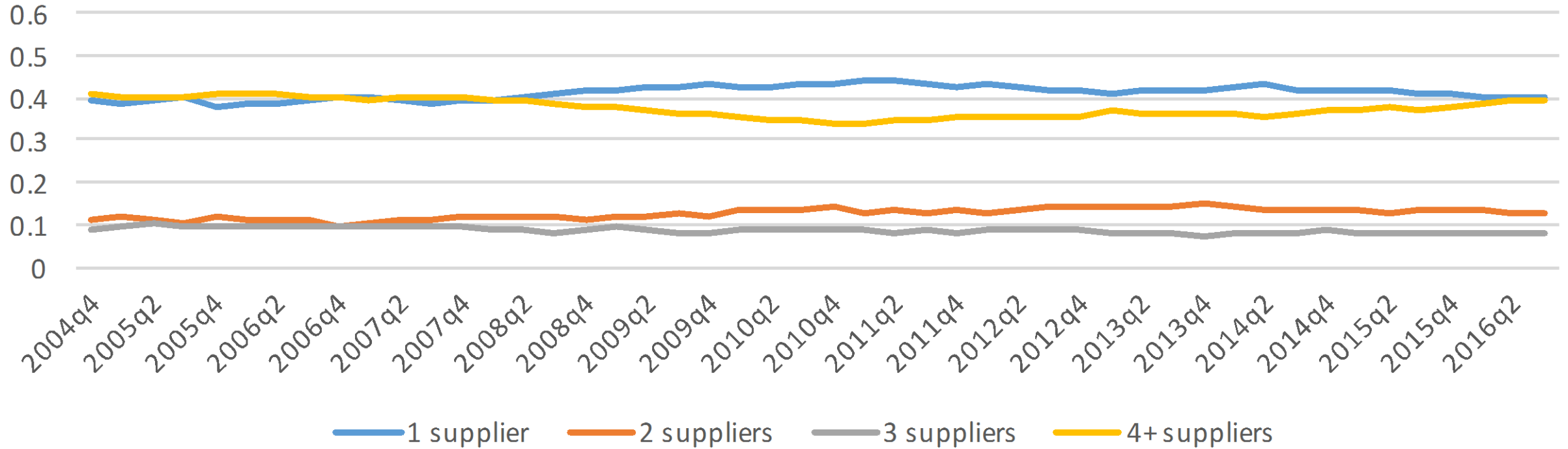
Median Number of Suppliers=3 pre-2008, 2 post-2008





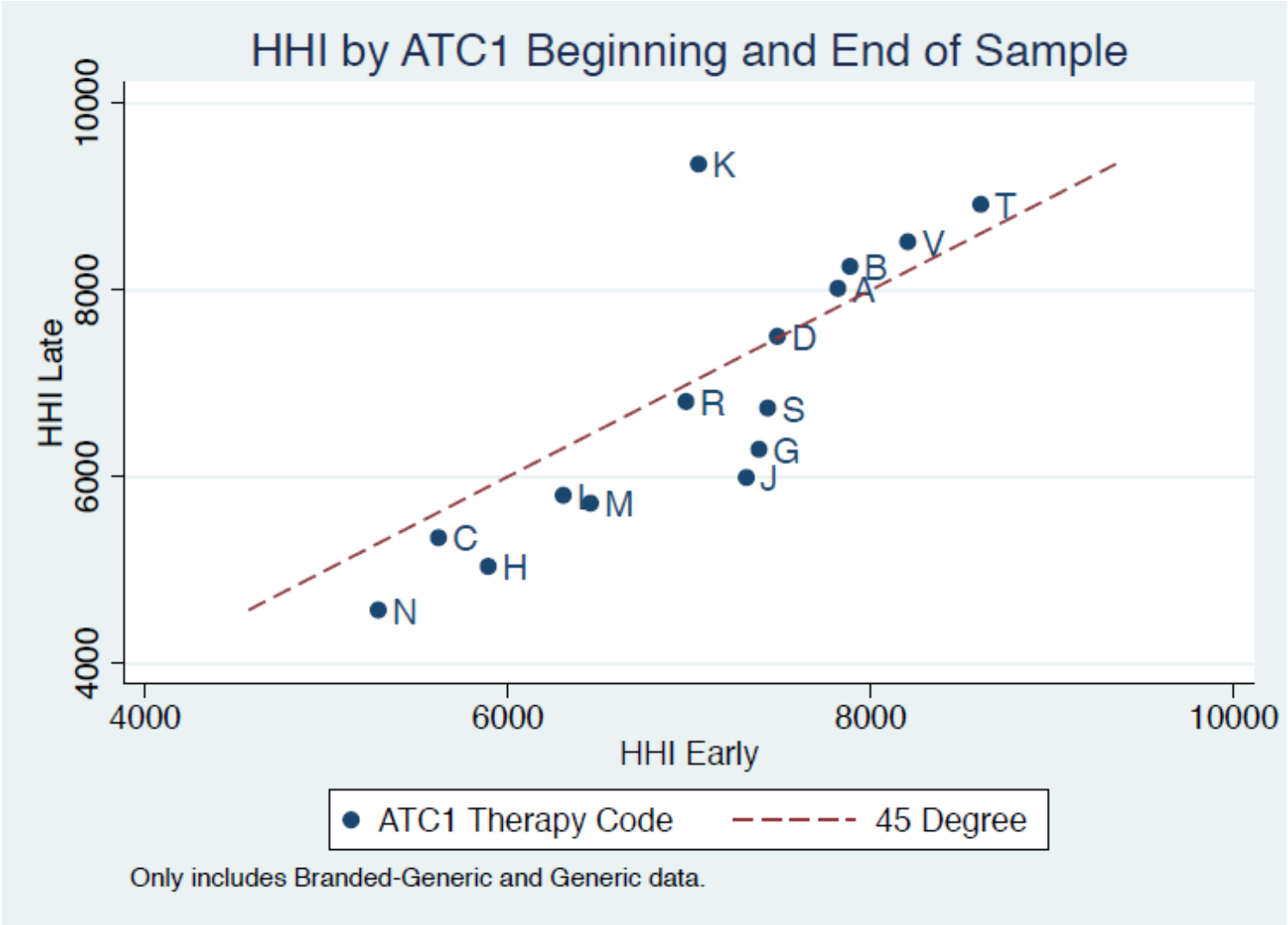
More than Half of all Generic Drug Markets are Supplied by 1 or 2 Manufacturers

Share of units sold by supplier count, all generic molecules





Slight Trend toward Lower Concentration, but HHI Levels Still High



Summary of Four Factoids on US Prescription Generic Drug Markets

- (1) Over the entire 2004Q4 – 2016Q3 sample, entry rates > exit rates, but in recent years, especially since 2012Q4 implementation of GDUFA I, entry rates are falling and exit rates are generally steady or slightly increasing.
- (2) For the most part, generic drug markets are small revenue markets, but the distribution is right skewed (with mean >> 75th percentile).
- (3) The median number of competitors in generic product market ranges between 2 and 3, in recent years steady at 2; 75th percentile ranges between 5 and 6. So generally, generic product markets have few competitors.
- (4) As measured by the HHI, concentration is declining in most therapeutic classes, but not all. However, in almost all classes the 2016 HHI is > 5,000, triggering usual DOJ/FTC antitrust concerns.

Preliminary Regression Results:

What Are Impacts of Limited Competition on Unit Prices?

- Regress exit rates, entry rates, and log unit (inflation adjusted) prices on log manufacturer counts or log HHI, route of administration (oral, injectable/infusible, other), therapeutic class, and regulatory regime indicator variables
- Four regulatory regimes (year is calendar, not fiscal):
 - Pre MMA = before MMA implementation 2004Q4 – 2005Q4.
 - MMA = after MMA implementation 2006Q1 – 2010Q1.
 - ACA = after ACA passage and implementation 2010Q2 – 2012Q3.
 - GDUFA = after GDUFA I implementation 2012Q4 thru 2016Q3.

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***	0.948***			
4_GDUFA	0.754***	0.897***			
ALL OTHERS		0.000	0.000	0.000	0.000
INJECTABLE		0.201	0.210	0.304*	0.346
ORAL		0.501***	0.504***	0.597***	0.897***

- In the Pre-MMA period, we observe the share of manufacturers exiting to be about 4.4% ($\exp^{1.467}$, constant term Column 1). (not shown).
- Compared to Pre-MMA levels, manufacturer exit appears to increase over time by .021 percentage points each quarter in the data (Column 3, time trend coefficient). (not shown).
- Manufacturing exits statistically increased by 0.339 percentage points after MMA passage, 0.816 percentage points after ACA passage and implementation and 0.754 percentage points after GDUFA implementation compared to the Pre-MMA period (see coefficients Column 1). These numbers are quite stable when route of administration controls are included (column 2).

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	-0.268			
3_ACA	-0.016	-0.102			
4_GDUFA	-0.399**	-0.630***			
ALL OTHERS		0.000	0.000	0.000	0.000
INJECTABLE		-0.426*	-0.424*	-0.475**	-0.605
ORAL		0.363*	0.364*	0.315	0.071

- Base level entry share of manufacturers amounts to 2.749% in the Pre-MMA period (not shown).
- Compared to Pre-MMA levels, manufacturer entry appears to decrease over time by 0.01 percentage points each quarter in the data (Column 3, time trend coefficient). (not shown).
- We also detect statistically significant declines in entry after MMA implementation amounting to 0.251 percentage points and after GDUFA passage amounting to 0.399 percentage points (Column 1) compared to the Pre-MMA period. The MMA and GDUFA negative impacts on generic entry share become larger in absolute value when route of administration controls are added (column 2).



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

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price	Log Price
Log Corp		-0.736***	-0.737***	-0.799***	-0.806***	-0.738***	-0.378***						
Log Mnf								-0.720***	-0.721***	-0.774***	-0.780***	-0.712***	-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***					

- Prices of generic drugs are observed to increase statistically significantly over time; after MMA implementation prices rise 0.101 percentage points, after ACA prices rise 0.401 percentage points, and after GDUFA implementation prices rise 0.751 percentage points (Column 1) compared to the Pre-MMA period.
- We also find prices negatively associated with larger counts of corporations (Columns 2-7) and manufacturers (Columns 8-13) – a one percent increase in corporation count results in a 0.736 percentage point fall in price and a one percent increase in manufacturer count results in a 0.720 percentage point fall in price.



Preliminary Implications (non-FDA related)

- With such limited competition, is it surprising prices have not risen more dramatically over time:
 - *Does this have something to do with increasing consolidation on demand side from PBMs, insurers, retail chains?*
- Anti-trust typically responsible for maintaining adequate competition in markets:
 - *Given that generic molecule markets typically involve less than \$10 million in annual sales revenues, the Hart-Scott-Rodino minimum threshold for required public reporting of acquisitions, currently at \$80.8 million, may often not be triggered:*
 - *M&A activity could result in molecule market monopolies or limited competition oligopolies without receiving any public scrutiny – use public health rather than dollar transaction threshold criteria?*
 - *Important that research address if these M&A activities are related causally to supply disruptions, price spikes.*

Additional Implications for FDA reform, Non-GDUFA related

- Commissioner Gottlieb recently announced expedited review of ANDAs for off-patent drugs with three or fewer active ANDAs. Given our results, many policy-related questions:
 - *Will suppliers pursue expedited review for ANDAs in product markets with limited competition?*
 - *If so, which ones? How many?*
 - *Impacts on price spikes of drugs with limited competition? Impacts on shortages?*
 - *Might the FDA aim to target expedited review to product markets that are important standard of care? Might FDA want to work with rare disease and patient advocacy groups to identify small markets whose high concentration has critical public health implications? A suggestion: use QuintilesIMS MIDAS global data to identify particularly worrisome limited competition markets.*

Additional Implications for FDA reform, Non-GDUFA related (cont.)

- Commissioner Gottlieb announced expedited review of ANDAs for drugs with no off-patent competitors:
 - FDA list: Total of 267 NDAs, 223 distinct or combination molecules. Mostly very old drugs – sample yielded mean age 39.17 years (launched in 1978), median age 38 years, and only about 25% were NMEs – most NDAs listed were reformulations of previously approved NDAs, so even older APIs than on the FDA list of NDAs.
 - QuintilesIMS 2017 data: 92 of 267 (34%) have zero sales in US.
 - ***i.e. There's likely a good reason there are no ANDAs – there's no market for most (but not all) of these very old drugs!***
 - *Suggests expedited review incentives will likely not attract much entry.*
 - Among existing markets, some may be orphans or standard of care medicines, recently subject to huge price increases. *Work with rare disease and patient advocacy groups to identify small markets whose high concentration/high price has critical public health implications?*

Limitations – Focus for Future Research

- Much M&A activity among generic firms in last decade. How to quantify this and track its effects on number of products and pricing of products in various therapeutic classes over time?
- What are the price and access implications of going from 3 to 2 competitors, 2 to 1 competitors?

Thank you!

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