

Small Revenue Concentrated Markets, Expedited Reviews, and Incentives to Ensure A Balance between Innovation and Access

Ernst R. Berndt, MIT Sloan School and NBER

Rena M. Conti, University of Chicago

Stephen J. Murphy, NBER

Washington DC, July 18, 2017

Acknowledgements and Disclaimers

- Mr. Berndt and Mr. Murphy acknowledge research support from the National Institutes of Health, National Institute on Aging, Grant R01AG043560, to the National Bureau of Economic Research. Ms. Conti acknowledges research support from The Commonwealth Fund and the American Cancer Society. We have benefited from extraordinary data support from Michael Kleinrock at QuintilesIMS, and from discussion of regulatory and legal issues with Karl R. Karst of Hyman, Phelps and McNamara PC.
- Any opinions and findings expressed here are those of the authors, and are not necessarily those of the institutions with whom they are affiliated, the research sponsors, or those providing us information.
- Research presented here is still in progress – please inquire of authors before citing and sharing.

Background on Recent Research

- Our presentation today is based in part on two currently unpublished manuscripts coauthored by Ernst R. Berndt (MIT Sloan and NBER), Rena M. Conti (University of Chicago) and Stephen J. Murphy (NBER) that will shortly be issued as working papers at the National Bureau of Economic Research, available at www.nber.org:
- “The Landscape of U.S. Generic Prescription Drug Markets, 2004-2016” July 2017, and
- “The Generic Drug User Fee Amendments: An Economic Perspective” July 2017.
- Our email contact addresses are eberndt@mit.edu, rconti@peds.bsd.uchicago.edu, and Murphystephenj@gmail.com.

Agenda

- Present results of characterizing the competitiveness of the US generic drug industry, focusing on trends in revenues per molecule, number of competitors per molecule, and exit and entry of manufacturers.
- In the second part of our presentation we will compare certain aspects of the Prescription Drug User Fee Act (PDUFA) of 1992 for branded products, with the Generic Drug User Fee Act of 2012 (GDUFA I), and with the preliminary proposed reauthorization of the user fee legislation, GDUFA II. We will also comment on implications of our research for the proposed expedited review of ANDAs in generic markets with limited competition.

Background to Empirical Work

- Generic drug market have commonly been characterized as encompassing a virtuous circle:
 - Extensive entry and price competition among generic manufacturers, facilitated by strong demand growth has resulted in 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 injectables and some old orals.
 - 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):
 - The larger the dollar sales pre-LOE, the greater the number of entrants post-LOE.
 - Generics commonly capture 80-90 percent of molecule sales within a year of post LOE.
 - As the number of entrants increases, average generic prices decline
 - Injectables, infusables and aerosols are not immune to these forces, although they are particularly prominent for oral solid formulations

Study Questions

- How competitive are US markets for generic drugs, and how might this competition vary over time and among specific drug therapeutic classes and types?
 - I.e., to what extent can one characterize the US generic drug industry as being highly concentrated and vulnerable to supply interruptions?
 - Has the GDUFA fee structure contributed to exacerbate concentration, and altered generic price trends?

Empirical approach

- Characterize market structure and relate market to molecule sales revenues and prices in the cross-section and over time 2004Q4 – 2016Q3.
- “Product market” defined 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
- Market structure quantified by manufacturer counts, entry, exit.

Data: QuintilesIMS National Sales Perspective (NSP) 2004Q3–2016Q3

- All molecules sold by manufacturer through all drug channels
 - Sample per year includes: Approximately 500-650 manufacturers, 1700 -2200 molecules.
- Manufacturers: unique “labeller” for each molecule-qtr.
- Total net sales and standard units sold by molecule-qtr.
- Patent status = NSP contains a data field denoting whether each molecule-qtr is “generic, “branded” or “branded generic”; generic \equiv multi-source generic plus branded generics containing that API
- Drug Route of Administration = oral solid tablets or capsules, injectables/infusibles and “other” (e.g. topicals, inhalants).
- Therapeutic class = World Health Organization’s 244 four-digit anatomic therapeutic classification, aggregated by QuintilesIMS into 15 therapeutic areas

Key measure definitions

- EntrantMnf = indicator variable if, immediately following two quarters of zero units and dollar sales, there are at least two quarters of positive unit and sales data of the molecule by the Mnf.
- ExitMnf = indicator variables if, immediately following at least two quarters of positive unit and sales data, there are at least two quarters of zero unit and sales data for the Mnf.
- EntrantMnf share(t) = $\sum_i \text{EntrantMnf}_i(t) / \text{NMnfi}(t)$.
- ExitMnf share(t) = $\sum_i \text{ExitMnf}_i(t) / \text{NMnfi}(t)$
- “Price” per unit = total net sales/standard units sold, inflation adjusted \$2016Q1 using the GDP deflator.

Four Regulatory Regimes

Note: “Year” Refers to Calendar not Government Fiscal Year

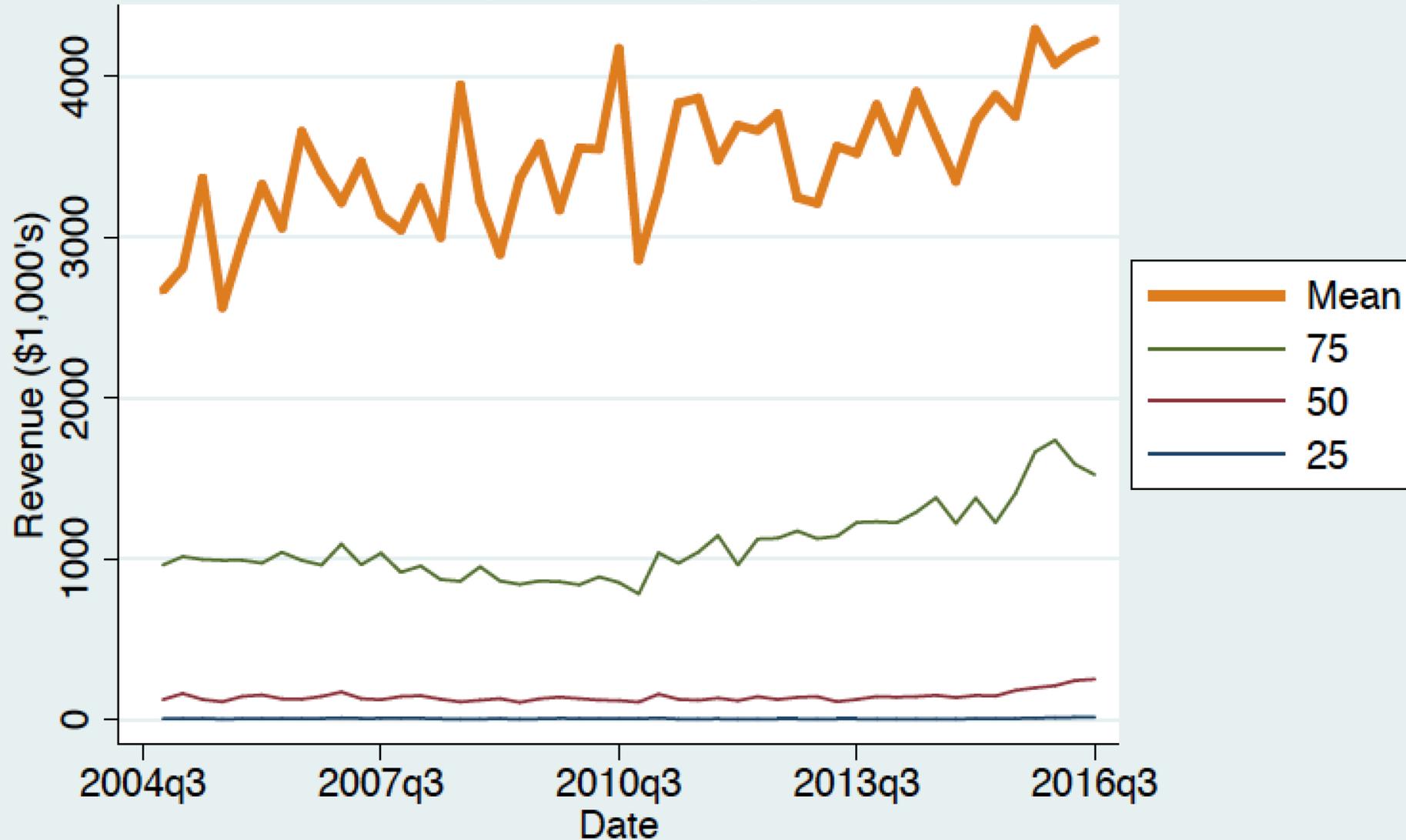
- Pre MMA = before MMA implementation 2004Q4 – 2005Q4
- MMA = after MMA implementation 2006Q1 – 2010Q1
- ACA = after ACA passage and implementation 2010Q2 – 2012Q3
- GDUFA = after GDUFA I implementation 2012Q4 thru 2016Q3

Part I: Analytical Methods to Characterize Generic Product Markets

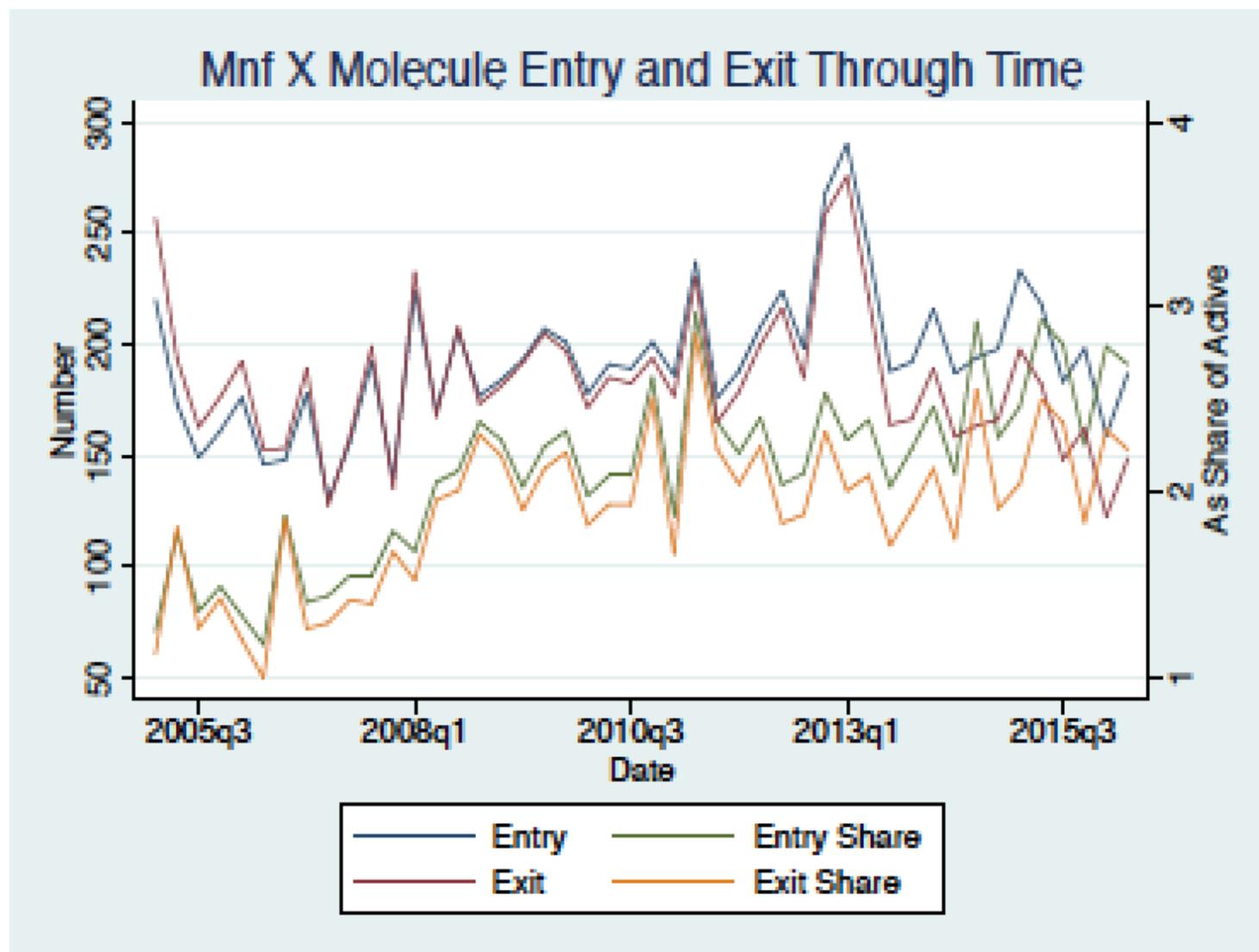
- Descriptive statistics:
 - Mean, median and interquartile range of sales revenue per molecule-mnf-qtr-yr.
 - Count of manufacturers entering and exiting markets.
 - Mean, median and interquartile range of manufacturers per molecule.
- Simple reduced form multivariate regressions estimated using OLS, generics only:
 - Manufacturer exit- and entry-share separately as a function of regulatory regime, patent status.
 - Logged molecule price levels as a function of regulatory regime.
 - Include controls for other drug characteristics, quarterly time passage and molecule fixed effects.
 - Molecule clustered standard errors.

Revenue per Molecule-Manufacturer Pair

Mean and Interquartile Range per Generic Mnf



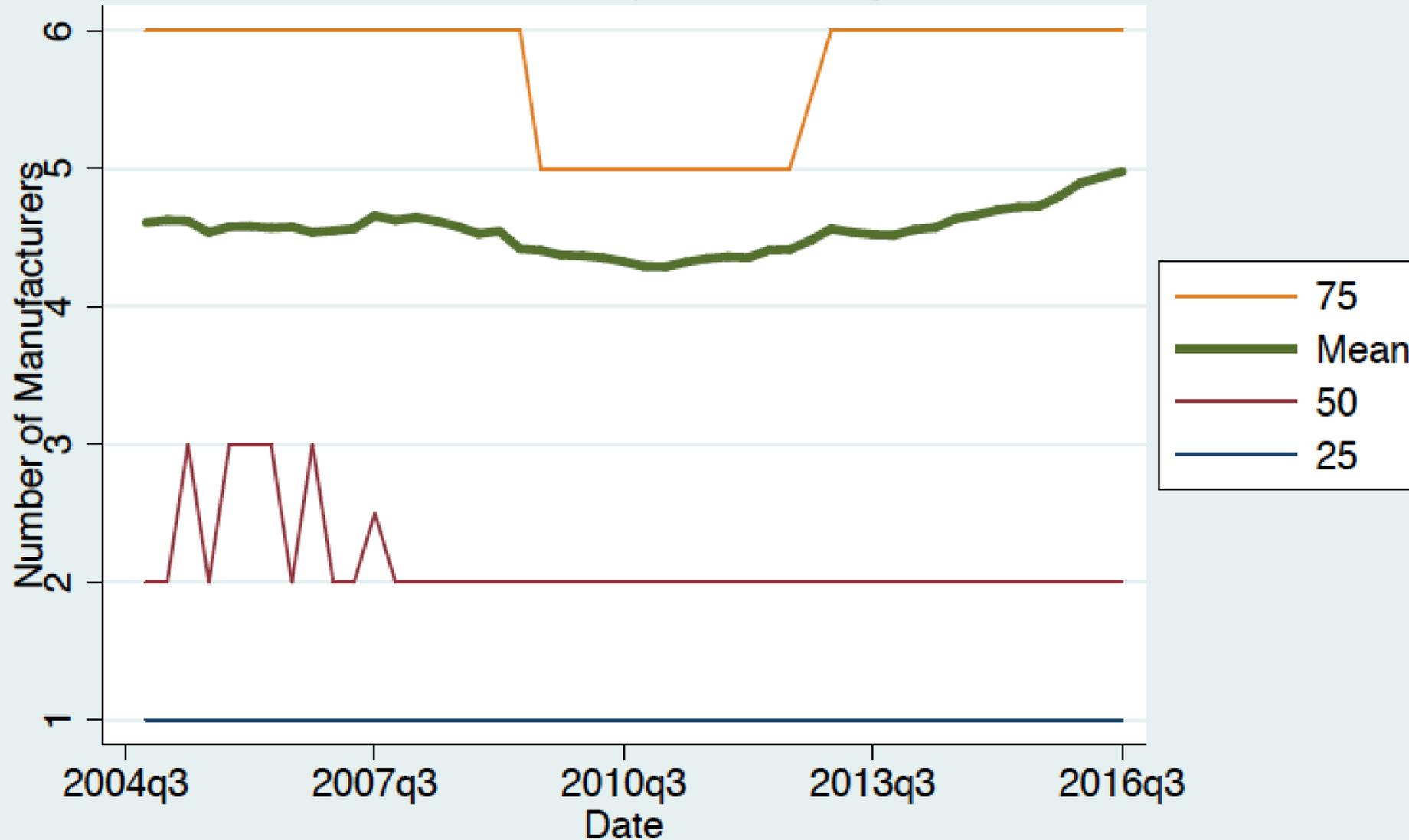
Only includes Branded-Generic and Generic data.



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.

Number of Generic Mnfs. Producing a Molecule

Mean and Interquartile Range



Only includes Branded-Generic and Generic data.

Share of units sold by supplier count, all generic molecules

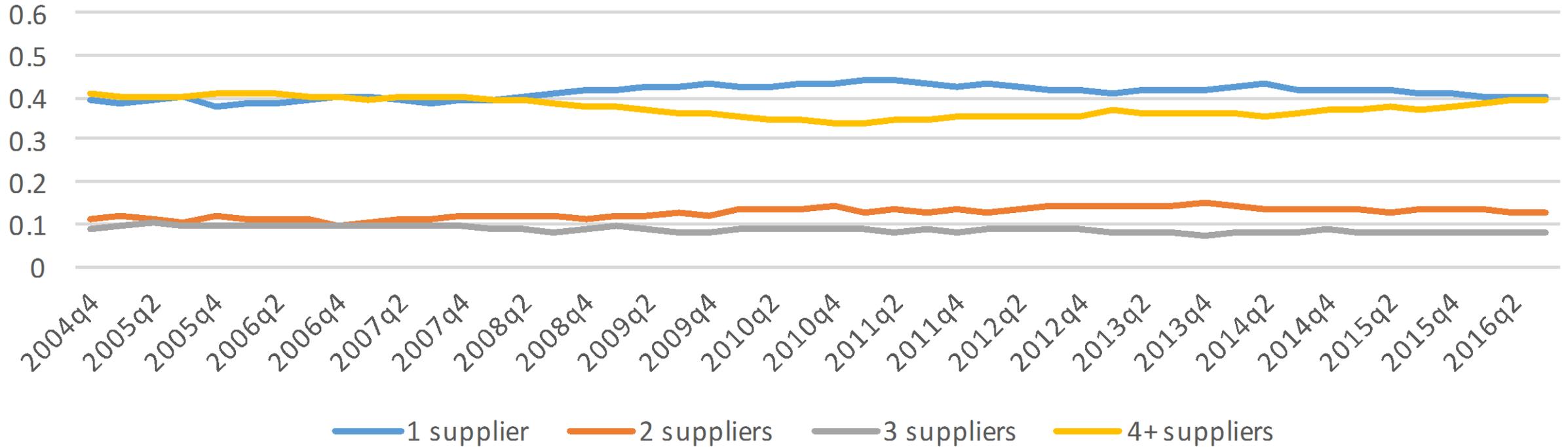


Table 3: Regression Results on Generic Exit Share

	(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 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.

Three Takeaways from this Research

- Quarterly sales revenue per quarter for a manufacturer/molecule are surprisingly small.
- Generics product markets generally have a small number of competitors (median=2).
 - Although entrants outnumbered exits through much of the sample, since 2013 these churn rates have converged. Could reflect impacts of patent cliff, consolidations, and barriers to entry and inducements to exit from GDUFA I.
- Prices of generic drugs are increasing over time, particularly after ACA and GDUFA implementation; positively correlated with reduced manufacturer counts, increasing concentration measures (not shown).

Preliminary Implications (non-FDA related)

- With such limited competition, 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 at \$80.8 million may often not be met.
 - M&A activity could result in molecule market monopolies or limited competition oligopolies without receiving public scrutiny – 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

Preliminary Implications (FDA-related)

- Part II of our Research: The Generic Drug User Fee Amendments of 2012 and their 2017 Proposed Reauthorization: An Economic Perspective

Aspects of the GDUFA I User Fee Structure

- Similar to PDUFA, GDUFA I had one-time application fees. But GDUFA I had annual facility fees, larger for FDF than for API facilities, and \$15K larger for foreign than domestic sites. No foreign-domestic fee distinction for PDUFA, and annual establishment but not annual facility fees for PDUFA.
- Because of importance of contract manufacturing organizations (CMOs) in the manufacture of generic drugs, GDUFA I had one-time Drug Master File (DMF) fee that ANDAs could reference, but not separate CMO fee from facility fee. No PDUFA analog.
- Unlike for PDUFA, with GDUFA the annual facility fees were due at the time the ANDA was submitted, rather than after the ANDA was approved.
- With median review times greater than 40 months in 2013, this required payment of four times the annual facility fee while ANDA submission was pending and before generic could be marketed a substantial cost to generic entrants. In GDUFA I, annual facility fees still assessed if product discontinued but not if withdrawn. *A very substantial barrier to entry and inducement to exit via withdrawal?*

APPLICATION AND GDUFA I PROGRAM USER FEES BY FISCAL YEAR

	ONE-TIME APPLICATION FEES			ANNUAL GDUFA I PROGRAM FEES			
Fiscal Year	ANDA	PAS	DMF	API-D	API-F	FDF-D	FDF-F
2013	\$ 51,520	\$ 25,769	\$ 21,340	\$ 26,459	\$ 41,458	\$ 175,389	\$ 190,389
2014	\$ 63,860	\$ 31,920	\$ 31,460	\$ 34,515	\$ 49,515	\$ 220,152	\$ 235,152
2015	\$ 58,730	\$ 29,370	\$ 26,720	\$ 41,926	\$ 56,926	\$ 247,717	\$ 262,717
2016	\$ 76,030	\$ 38,020	\$ 42,170	\$ 40,867	\$ 55,867	\$ 243,905	\$ 258,905
2017	\$ 70,480	\$ 35,240	\$ 51,140	\$ 44,234	\$ 59,234	\$ 258,646	\$ 273,646
CAGR	8.2%	8.1%	24.4%	13.7%	9.3%	10.2%	9.5%

Notes: ANDA is Abbreviated New Drug Application, PAS is Prior Approval Supplement, DMF is Drug Master File, API is Active Pharmaceutical Ingredient, FDF is Final Dosage Form, the suffixes D and F are domestic and foreign, respectively, and CAGR is compounded annual growth rate.

From GDUFA I to GDUFA II: Desired Changes

- *How to make FDA user fee revenues more stable?*
- Answer: Assess them annually on *stock* of approved ANDAs, not on *flow* of new ANDA/PAS submissions. Fees called annual ANDA program fees.
 - Eliminate PAS fees entirely – volatile, often a response to an FDA request.
- Recognize small business concerns:
 - Devise annual program fee based on total number of ANDAs held by each sponsor.
 - Tentative agreement that all ANDA sponsors with one or more approved ANDAs would pay a tiered annual program fee, depending on the number of ANDAs owned by an ANDA sponsor and its affiliates: Large (≥ 20 ANDAs), Medium (6 – 19 ANDAs) and Small (1 – 5 ANDAs).
 - Sponsors with large portfolio pay full annual program fee, medium 40% of full fee, and small 10% of full fee.
 - Note huge economies of scope for large ANDA holders.

GDUFA I v. GDUFA II Fee Structure

Fee Category	GDUFA I		GDUFA II	
1-time Fees:				
• ANDA Application	✓	24%	✓	33%
• DMF Application	✓	6%	✓	5%
Annual Program Fees:				
• API Facility	✓	14%	✓	7%
• FDF Facility	✓	56%	✓	20%
• CMO Facility	Same as FDF		✓	One-third FDF
• ANDA Holder	N/A		✓	35%
• Small (1-5 ANDAs)	N/A		✓	One-tenth Large
• Medium (6-19)	N/A		✓	Four-tenths Large
• Large (20+)	N/A		✓	Full Fee

From GDUFA I to GDUFA II: New Data Needs

- Issue: FDA estimated that in 2016 there were about 10,000 approved ANDAs (but also knew “many approved ANDAs are not marketed”) – *how to find out who owned what ANDAs, and were they still being actively marketed?*
 - FDA action: Use Orange Book to identify ANDA owners, ask the apparent ANDA holders as of November 14, 2016 to inform FDA by February 2017 what ANDAs they owned and their manufacturing status.
 - Only 6.8% (46 of 676) identified ANDA holders responded to November 2016 FDA request. In April 2017 FDA published the lists of claimed and unclaimed ANDAs as of March 10, 2017. Respondents were very different from non-responders.

Respondents Claiming ANDA Ownership

- Respondents were disproportionately holders of large ANDA portfolios:
 - 28.3% (13 of 46) responding sponsors each claimed ownership of portfolios consisting of > 150 ANDAs -- accounting for 6,014 of the 7,089 (84.8%) of all claimed ANDAs as of March 10, 2017.
 - Ten largest sponsors claimed 5,483 or 77% of the 7,089 total claimed ANDAs:
 - Teva Pharmaceuticals USA Inc (1,609 ANDAs), Mylan Inc (662), Novartis Corporation (647), Sun Pharmaceuticals (593), Hikma Pharmaceuticals PLC (494), Endo International PLC (378), Aurobindo Pharma Ltd (314), Apotex Inc (281), Pfizer Inc (279), and Perrigo Company PLC (226).

Two Takeaways Regarding GDUFA I and II

- It appears that the US generic drug industry consists of a very large number of sponsors with small ANDA portfolios, and a small number of sponsors with very large portfolios.
 - More evidence of high concentration and supply vulnerabilities.
- The causes of this bifurcated industry structure pre-date GDUFA, but the GDUFA fee structure embodies substantial economies of scope in annual program fees, and substantial economies of scale in facility and DMF fees.
 - The GDUFA fee structure likely exacerbates barriers to entry and incentives to exit.
 - Commissioner Gottlieb and the President's budget entail large increases in generic user fees beyond those contemplated in the preliminary proposed GDUFA II fee structure. Will the FDA's increased reliance on generic user fees further exacerbate these incentives, raising entry barriers and heightening incentives to exit, thereby increasing concentration and prices?

Additional Implications for FDA reform, Non-GDUFA related

- Commission Gottlieb announced expedited review of ANDAs for off-patent drugs without generics, or with three or fewer active ANDAs:
 - FDA list of off-patent drugs without any generics: Total of 267 NDAs, 223 distinct or combination molecules. Very old drugs – sample yielded mean age 39.17 years (launched in 1978), median age 38 years, and only about 25% were NMEs – most were reformulations of previously approved NDAs, so even older APIs than on the FDA list.
 - QuintilesIMS 2017 data: Only 92 of 267 (34%) have positive sales in US. There's a good reason there are no ANDAs – there's no market for most (but not all) of these very old drugs! Some rare ones are standard of care medicines, recently subject to huge price increases.
 - Suggests majority of off-patent drugs without generics have minimal demand, and expedited review incentives will therefore likely not attract new generic entry. Can expedited review be targeted to product markets that have small (≤ 2 or 3) number of active ANDA competitors, but are important standard of care? Minimal number of standard or extended units sold quarterly?
- Given our results, many questions:
 - *Will suppliers pursue expedited review for these drugs? Which ones? Which suppliers (large multiproduct firms or small firms? Foreign or domestic?)*

Thank you!

- Forthcoming working papers on which this presentation has been based will be available shortly from the National Bureau of Economic Research, www.nber.org.
- Contact us at:
 - eberndt@mit.edu
 - rconti@peds.bsd.uchicago.edu
 - Murphystephenj@gmail.com