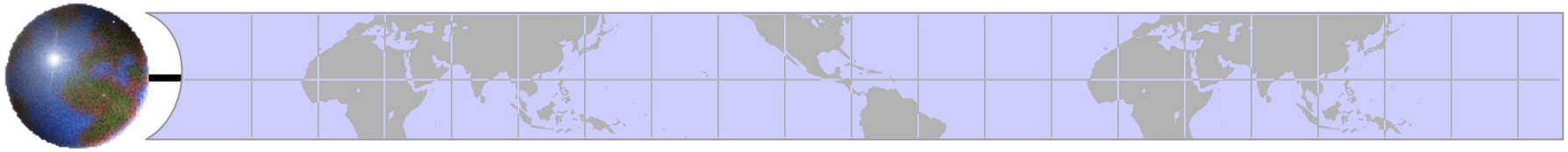


Generic Competition and the Incentives for Early-Stage Pharmaceutical Innovation

Lee Branstetter, Carnegie Mellon University, Peterson Institute, NBER

Chirantan Chatterjee, Indian School of Business, Hoover Institution

Matthew Higgins, University of Utah, NBER, Max Planck Institute

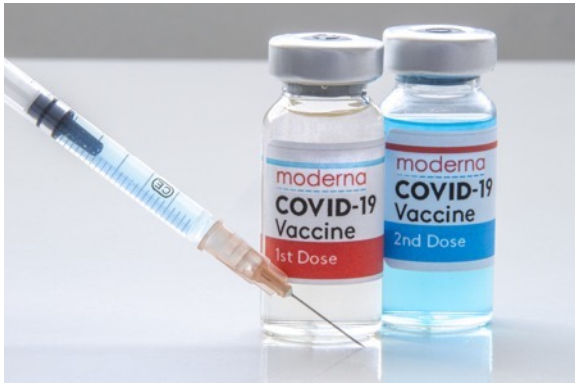
Pharmaceutical innovation has had an enormous impact on human welfare

- Nordhaus (1999) argues that the advances in human welfare generated by better medical science over the last half century have been equal in value to all of the consumption increases from all other sources put together.

- Fuchs (1982) and Lichtenberg (2001, 2004, 2007) suggest that much of the improvement in health is due to humanity's expanding pharmaceutical arsenal.

- The U.S. markets rules and regulations have played a disproportionately important role in promoting this innovation.

The National AIDS Memorial Quilt, Washington, DC, 1992



Public policy changes have expanded generic penetration in U.S. drug markets since the late 1990s

- Important legal decisions have made generic entry easier, faster, and more financially attractive, sometimes by limiting patent strength or breadth.
  - Mova v. Shalala (1998); KSR v. Teleflex (2006); MedImmune v. Sun Pharma (2007)

- FDA policy shifts have expedited generic entry
  - Starting in 2000, the FDA began approving "Paragraph-IV" generic entry upon a first court ruling in favor of the generic manufacturer (instead of waiting for appeal decisions)

- Legislation has expedited generic entry
  - The Medicare Act of 2003 limited branded pharmaceutical firms to one 30-month stay per product.

As generic penetration has risen, the U.S. drug market has undergone a profound shift

- Generic penetration is increasingly pervasive in the U.S. market.
  - By the mid-2010s, generics made up 84%-88% of prescription drug sales
- Generic entry is occurring at an earlier stage in the product life cycle.
  - By the end of the 2000s, Paragraph IV certification accounted for more than 40% of generic entry
- The "consumer" welfare gains from rising generic penetration are substantial.
  - Branstetter et al. (2016) document substantial gains from early generic entry into hypertension drugs, but the fraction of these gains that actually goes to consumers is unclear.
  - The increase in downstream surplus comes mostly at producers' expense, with little expansion of social surplus
- What impact, if any, is this having on pharmaceutical innovation?

Expanding generic entry reduces new drug development in the same therapeutic category

- We find a sizable, negative relationship between generic entry and early-stage pharmaceutical research activity.
  - A 10% increase in generic penetration is associated with a decrease in the flow of early-stage innovations of about 6-7%.
  - A 10% increase in generic penetration is associated with a decrease in the flow of novel (first in class) innovations of nearly 6%.

- The effect is robust to a large number of controls and alternative specifications.
  - Use of plausibly exogenous instruments for shifts in generic penetration
  - Inclusion of market*year fixed effects
  - Focus on first-in-class innovations
  - Use of a dynamic, GMM-specification that allows for serial correlation
  - Several "placebo" tests

Expanding generic entry shifts the *direction* of drug development toward biotech drugs

- As generic penetration increases, the *nature of pharmaceutical innovation shifts* from chemical-based (small molecule) to biologic-based (large molecule) products.

- The overall level of early-stage innovation is *not declining*. Generic entry appears to influence where and how pharmaceutical innovation is conducted.

- Cheaper drugs now, more expensive drugs later?

We use Pharmaprojects data to measure pharmaceutical innovation at the firm-product-year level…

$$Inn_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2 Price_{ijt-1} + \beta_3 Tech\ Opp_{jt-1} + \beta_4 Tech\ Challenge_{ijt-1} + \beta_5 Product_{ijt-1} + \beta_6 LatePipe_{ijt-1} + \beta_7 FirmSize_{it} + \varepsilon_{ijt}$$

- Inn_{ijt} (Pharmaprojects): Count of compounds in preclinical or Phase I clinical testing by firm *i* in therapeutic market *j* in year *t*.

- Unit of observation: ATC2

ATC N – Central Nervous System

- N1 Anesthetics
- N2 Analgesics
- N3 Antiepileptics
- N4 Anti-Parkinson
- N5 Psycholeptics
- N6 Psychoanaleptics
- N7 Other CNS drugs

We use IQVIA MIDAS data to track generic competition across firms, product markets, and time

$$Inn_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2 Price_{ijt-1} + \beta_3 Tech\ Opp_{jt-1} + \beta_4 Tech\ Challenge_{ijt-1} + \beta_5 Product_{ijt-1} + \beta_6 LatePipe_{ijt-1} + \beta_7 FirmSize_{it} + \varepsilon_{ijt}$$

- $Generic_{ijt-1}$ (IQVIA MIDAS): Generic penetration faced by firm *i* in therapeutic market *j* in year *t-1*.
- Incorporates the impact of generic entry though all legal channels.
- Impact of generic competition remains even after controlling for market competition between branded products.

We use comprehensive PubMed data to track shifts in "scientific opportunity"…

$$Inn_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2 Price_{ijt-1} + \beta_3 Tech\ Opp_{jt-1} + \beta_4 Tech\ Challenge_{ijt-1} + \beta_5 Product_{ijt-1} + \beta_6 LatePipe_{ijt-1} + \beta_7 FirmSize_{it} + \varepsilon_{ijt}$$

- $TechOpp_{jt-1}$: IQVIA NDTI to create an ICD-9 / ATC4 concordance.
- Use ICD-9 keywords to obtain publications from PubMed.
- Gathered citations for all of these articles from Scopus.
- Data created at ATC4 but aggregated to ATC2 to create $TechOpp_{jt-1}$
- 6.5 million journal articles between 1950 and 2010. One-to-many relationship with ATCs yields 20.9 million raw article counts with over 345 million forward citations.

The potential problem lurking in our error term…

- We have unobserved research productivity lurking in the error term.
- A decline in research productivity leads to a decline in drug introductions and, eventually, a rise in generic competition.
- Could our results be an artifact of omitted variable bias?

We employ empirical strategies to contend with this challenge…

$$Inn_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2 Price_{ijt-1} + \beta_3 Tech\ Opp_{jt-1} + \beta_4 Tech\ Challenge_{ijt-1} + \beta_5 Product_{ijt-1} + \beta_6 LatePipe_{ijt-1} + \beta_7 FirmSize_{it} + \varepsilon_{ijt}$$

- We employ a GMM specification with a lagged dependent variable
- We can employ a set of "placebo tests"
- We can instrument for G_{ijt}

A rise in generic penetration depresses new drug development…

	NEGATIVE BINOMIAL	OLS	POISSON
Generic$_{ijt-1}$: Generic market penetration	-1.214*** (0.181)	-0.090*** (0.09)	-1.189*** (0.196)
Firm Fixed Effects	Y	Y	Y
Year Fixed Effects	Y	Y	Y
Market Fixed Effects	Y	Y	Y
Year*Market Fixed Effects	Y	Y	Y
N	29,514	29,514	29,514

Robustness checks with IVs confirm this result

Variables	(1)	(2)	(3)	(4)	(5)
	OLS	IV	IV	GMM	GMM
	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$	−0.097***	−0.333***	−0.370***	−0.364 ***	−0.449***
	(0.018)	(0.170)	(0.196)	(0.136)	(0.134)
Inn_{ijt-1}				0.552	0.655***
				(0.100)	(0.0922)
$Price_{jt-1}$		−0.000***		0.000	0.000715
		(0.000)		(0.001)	(0.00135)
$Tech\ Opp_{jt-1}$		0.007		0.001	0.000413
		(0.003)		(0.002)	(0.00228)
$Tech\ Challenge_{ijt-1}$	0.317***	0.350***	0.333***	0.613	0.593
	(0.037)	(0.079)	(0.068)	(0.528)	(0.539)
$Product_{ijt-1}$	0.085***	0.081***	0.092***	0.307	
	(0.015)	(0.015)	(0.015)	(0.138)	
$Late\ Pipe_{ijt-1}$	0.073	0.100***	0.102***	0.450	
	(0.060)	(0.026)	(0.023)	(0.370)	
$Firm\ Size_{it}$	0.002	0.008***	0.010***	0.000*	0.000
	(0.001)	(0.002)	(0.002)	(0.000)	(0.000)
Constant	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y
ATC1 FE	N	Y	Y	N	N
ATC1 × Year FE	N	Y	N	N	N
ATC2 FE	Y	N	Y	Y	Y
ATC2 × Year	Y	N	Y	N	N
First-stage F		125.88	43.12		
R^2/Wald X^2	0.263	0.155	0.207	1817.72	1745.58
Observations	29,514	29,514	29,514	21,089	21,089

A rise in generic penetration induces firms to shift from small molecule drug development to biologics

$$CI_{ijt} - BI_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2 (Tech\ Opp_{jt-1}) + \beta_3 (CTech\ Challenge_{ijt-1} - BTech\ Challenge_{ijt-1}) + \beta_4 (CProduct_{ijt-1} - BProduct_{ijt-1}) + \beta_5 (CLate\ Pipe_{ijt-1} - BLate\ Pipe_{ijt-1}) + \beta_6 FirmSize_{it} + \varepsilon_{ijt}$$

Variables	(1)	(2)	(3)	(4)	(5)	(6)
	IV	IV	OLS	OLOGIT	OLOGIT	OPROBIT
	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$
$Generic_{ijt-1}$	−0.445**	−0.478**	−0.328***	−2.084***	−2.098 ***	−1.038***
	(0.217)	(0.192)	(0.025)	(0.117)	(0.119)	(0.062)
$Price_{jt-1}$	−0.000***			−0.002***	−0.002***	−0.001***
	(0.000)			(0.000)	(0.000)	(0.000)
$Tech\ Opp_{jt-1}$	0.006			0.025***	0.025***	0.014***
	(0.004)			(0.006)	(0.006)	(0.003)
$diff(Tech\ Challenge_{ijt-1})$	0.164***	0.134***	0.138***	2.988***	3.014***	1.533***
	(0.026)	(0.022)	(0.024)	(0.277)	(0.275)	(0.135)
$diff(Product_{ijt-1})$	0.056***	0.031***	0.032***	1.160***	1.159***	0.511***
	(0.009)	(0.007)	(0.008)	(0.111)	(0.110)	(0.048)
$diff(Late\ Pipe_{ijt-1})$	0.226***	0.177***	0.183***	−1.004***	−0.996***	−0.430***
	(0.021)	(0.019)	(0.018)	(0.155)	(0.155)	(0.070)
$Firm\ Size_{it}$	0.002	0.003	0.003	0.015	0.018	0.007
	(0.002)	(0.002)	(0.002)	(0.013)	(0.013)	(0.007)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	N	N	Y	Y	Y
ATC1 × Year FE	Y	N	N	N	Y	Y
ATC2 FE	N	Y	Y	N	N	N
ATC2 × Year FE	N	Y	Y	N	N	N
First-stage F	29.65	29.47				
R^2/Pseudo R^2	0.443	0.542	0.546	0.366	0.369	0.332
Observations	29,514	29,514	29,514	29,514	29,514	29,514

Conclusions and implications

- Evidence suggests that increases in generic penetration lower early-stage innovative activity (within ATC2 categories).
- Aggregate innovative activity has not declined…
- Increases in generic penetration appear to drive a shift away from chemicals-based innovation toward biologic-based innovation.
- Cheaper drugs today, more expensive drugs tomorrow?