Challenges in Maintaining Competition in Small Generic Drug Markets

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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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- 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 – comments welcomed, manuscripts currently under peer review.

Background on Recent Research

- Our presentations today are based in part on two currently unpublished manuscripts coauthored by Ernst R. Berndt (MIT Sloan and NBER), Rena M. Conti (University of Chicago) and Stephen J. Murphy (NBER) that have recently been issued as working papers at the National Bureau of Economic Research, available online at www.nber.org:
- Professor Berndt will draw on "The Generic Drug User Fee Amendments: An Economic Perspective" NBER Working Paper No. 23642, August 2017
- Professor Conti will base her presentation on "The Landscape of U.S. Generic Prescription Drug Markets, 2004-2016" NBER Working Paper No. 23640, July 2017

Agenda – Competition in US Generic Drug Markets

- Professor Berndt -- Background – based on FDA data: The Generic Drug User Fee Amendments of 2012. Shifting global manufacturing to ex-US sites, with most generic manufacturers marketing very small portfolios of drugs (requires approval of Abbreviated New Drug Applications – "ANDAs"). What are the economic incentives embodied in the fee structure of GDUFA I and GDUFA II?
- Professor Conti: Analyses of Economic Product Data from QuintilesIMS 2004Q3 – 2016Q2. Examine actual historical patterns of generic manufacturer entry and exit and impacts on US market outcomes (prices, spending, revenues, access).
- Policy Discussion.

Events Leading to Generic Drug User Fee Amendments ("GDUFA I") in 2012

- The number of generic drug applications (known as Abbreviated New Drug Applications, or "ANDAs") submitted to FDA for review, and number of foreign facilities making active pharmaceutical ingredients ("APIs") or finished dosage forms ("FDFs") grew rapidly in 2000-2010, in part because of extraordinary number of blockbuster drugs experiencing loss of exclusivity ("LOE") and facing patent cliff in 2011-2012, as well as general increase in off-shoring outsourcing
- ANDA review workload at FDA increased substantially without comparable growth in FDA workforce, resulting in growing backlog of submitted but not fully reviewed ANDAs, delaying entry for industry and lower generic prices for payers.
- Industrial poison melamine manufactured in China found in pet food in US in 2007, killing hundreds of U.S. cats and dogs. Then in 2008 at least 81 deaths were linked to adulterated raw heparin ingredient made in China.
- These events generated FDA, industry and Congressional consensus: With manufacturing of FDF, and especially of API, increasingly outsourced to ex-US, the FDA needs more reviewers and inspectors, funded substantially by user fees.

FDA Experience with User Fee Programs

- 1992 passage of Prescription Drug User Fee Act ("PDUFA")
- Bargain: In exchange for collecting somewhat predictable user fee revenues not subject to uncertain annual Congressional budget negotiations, FDA agreed to give New Drug Application ("NDA") review feedback to NDA sponsors within specified time frames, and under certain conditions, promised to expedite review times
- Three types of user fees in PDUFA: One time assessments for NDAs/Biologics License Applications ("BLAs") and their supplements, and annual fees for establishments and products. One-time assessments due at time of NDA/BLA submission, but annual fees not assessed until NDA/BLA has been approved
- Congress required that PDUFA be re-authorized every five years (PDUFA II in 1997, PDUFA III in 2002, PDUFA IV in 2007, and PDUFA V due for reauthorization in 2012) – latter simultaneous with design and implementation of GDUFA I

TABLE 1: PDUFA V Fee Schedule for FY 2013

NDA/BLA Application One-Time Assessments Due At Submission:	
Requiring clinical data	$1,958,800
Not requiring clinical data	$979,400
Supplements requiring clinical data	$979,400
Establishment Annual Fees	$526,500
Product Annual Fees	$98,380

How Valuable Was PDUFA Precedent for Designing and Implementing GDUFA I?

- Limited relevance: New drugs are novel molecules, so NDA/BLAs require considerably more clinical data concerning safety, efficacy and labeling than is the case for molecules that have been on the market for a decade or more and have an established safety and efficacy track record under approved labeling – ANDA review less rigorous clinically, requires only establishing bioequivalence and compliance with current good manufacturing practices ("cGMP")
- Brands with patent protection typically market intensively – DTC, journals, detailing – all monitored by Office of Prescription Drug Promotion at FDA. Generics typically don't devote much effort to marketing – notify providers of product availability, compete primarily on price and supply assuredness. FDA oversight and monitoring of marketing by generic firms much different than that for branded products

How Valuable Was PDUFA Precedent for Designing and Implementing GDUFA I? (cont'd)

- So NDA/BLA focus on product and labeling information was essentially inapplicable to ANDAs. Rather, ANDA focus was primarily on manufacturing issues
- FDA aware of increased ex-US outsourcing by generic (and, to a lesser extent) brand manufacturers to contract manufacturing organizations (CMOs), particularly to Central and Eastern Asia, Eastern Europe and Latin America
- Recall melamine and heparin product adulterations manufactured in China
- Prior to GDUFA, FDA was required to inspect *domestic* human generic drug manufacturers every two years, but no such requirement existed for *foreign* manufacturers. Congress and industry sought inspection parity between domestic and foreign facilities – but foreign inspections more costly to FDA
- Note that with PDUFA, there was no distinction in user fees between domestic and foreign establishments (see Table 1 slide). Apparently domestic-foreign manufacturing issues an issue for generics, but not for brands.

Data Needed to Design and Implement GDUFA I

- How ANDA holders manufacture generic drugs is varied: (i) in-house for both API and FDF; (ii) at facility site same as or different from headquarters; (iii) in-house FDF but outsourced API; (iv) outsourced both API and FDF; (v) not an ANDA holder but instead just a CMO to off-shore entities – FDA needed accurate and up-to-date data on detailed manufacturing operations
- Problem: FDA didn't know which ANDA holders were actively marketing, and how their manufacturing operations were organized, and if not an ANDA holder, how CMO operations were structured
- Solution: GDUFA I legislation mandated that certain sites and organizations initially identified in an ANDA submission or supplement provide info to the FDA annually between May 1 and June 1, i.e. to self-identify themselves
- Self-identification necessary to determine universe of facilities required to pay user fees, and to promote global supply chain transparency and prioritize manufacturing facility inspection operations
- Voluntary self-identification modestly successful having low response rate, but mandatory disclosure now a feature of GDUFA II reauthorization signed August 18, 2017

Number of Domestic and Foreign API and FDF Manufacturing Sites are Declining: Generic Drugs Are NOT Made in America!

FACILITY COUNTS AND LOCATIONS FROM

ANNUAL SELF-DENTIFICATION RESPONSES TO FDA

	Finished Dosage Form (FDF) Facilities			Active Pharmaceutical Ingredient (API) Facilities			Total Number of Facilities			
Fiscal Year	Domestic	Foreign	% Foreign	Domestic	Foreign	% Foreign	All	Domestic	Foreign	% Foreign
2013	325	433	57.1%	122	763	86.2%	1643	447	1196	72.8%
2014	315	433	57.9%	128	775	85.8%	1651	443	1208	73.2%
2015	271	410	60.2%	103	692	87%	1476	374	1102	74.7%
2016	283	422	59.9%	115	721	87.3%	1541	398	1143	74.2%
2017	255	420	62.2%	101	688	87.2%	1464	356	1108	75.7%
Mean	290	424	59.5%	114	728	86.7%	1555	404	1151	74%

Table 3: Application and GDUFA I 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%

Economic Incentives Embodied in GDUFA I Fee Structure: I

- Annual facility fees due at time of ANDA submission, not approval – with long approval times, considerable up-front financial commitment, particularly for small firms – discourages entry?
- If approved ANDA discontinued but not withdrawn, ANDA holder must still pay annual facility fees – not so if withdrawn. Encourages exit?
- New ANDA holders not having in-house API or FDF facilities can avoid annual API or FDF facility fees by outsourcing API or FDF facilities to CMOs
- For ANDA holders already having multiple API and FDF facilities and having spare capacity, incentives to become a CMO for other ANDA holders without incurring additional annual API or FDF facility fees – can exploit economies of scale and of scope

Economic Incentives Embodied in GDUFA I Fee Structure: II

- If single CMO can manufacture same API or FDF molecule for several ANDA holders, pay only one API or FDF annual facility fee, all made possible by previously paying a single DMF fee – exploit economies of scale. This can lead to highly concentrated manufacturing of a product, leading to supply vulnerabilities and shortages.
- Strategic consolidation issues involving governance and corporate affiliation also emerge from the GDUFA fee structure
- ANDA application fees at $70K a small fraction of NDA/BLS application fee of >$1.5 million, but annual FDF facility fees of around $200K a larger portion of PDUFA $500K annual establishment fee. Note that while PDUFA V has an annual product fee, GDUFA I does not.

WHILE MOST GENERIC FIRMS HAVE SMALL PORTFOLIOS OF ANDAs, THERE ARE A SMALL NUMBER OF BEHEMOTH PORTFOLIO HOLDERS

TABLE 5: ANDA PORTFOLIO SIZE AND OWNERSHIP DISTRIBUTION

AS OF SEPTEMBER 8, 2017

ANDA PORTFOLIO SIZE	NO. OF SPONSORS	SHARE OF SPONSORS	NO. OF ANDAS HELD	SHARE OF ANDAS HELD
1-5	306	71.7%	603	6.0%
6-10	35	8.2%	266	2.6%
11-50	52	12.2%	1181	11.7%
51-150	18	4.2%	1540	15.2%
151-300	9	2.1%	1816	18.0%
>300	7	1.6%	4700	46.5%
TOTALS	427	100.0%	10106	100.0%

Who Are the Behemoth ANDA Portfolio Owners in 2017?

1. TEVA Pharmaceuticals USA	1,569 ANDAs
2. Mylan Inc.	699
3. Novartis Corporation (Sandoz)	649
4. Sun Pharma	580
5. Hikma Pharmaceuticals PLC	498
6. Endo International PLC	378
7. Aurobindo Pharma LTD	327
8. Apotex Inc	288
9. Pfizer Inc (Hospira, Greenstone)	262
10 Perrigo Company PLC	228
Total Top 10	5,478 (54.2% of total 10,106 ANDAs)

Comparing GDUFA II (signed 8/18/17) and GDUFA I (implemented 1992)

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CAGR	8.2%	8.1%	24.4%	13.7%	9.3%	10.2%	9.5%

2018 $ 171,823 $0 $47,829 $45,367 $60,367 $211,087 $226,087

New in GDUFA II: Annual domestic (foreign) CMO facility fee of $70,362 ($85,302). No PAS.

New in GDUFA II: Annual program fees for small (1-5 ANDAs), medium (6-19), and large (>19):

2018 Program Fee: $159,079 $636,317 $1,590,792

Note that with 1,569 ANDAs, Teva is assessed a per ANDA annual program fee of about $1,014, while the about 150 sponsors with only one ANDA are each assessed a per ANDA program fee of about $160,000, implying enormous scale economies, incentivizing M&A consolidation.

LIMITATIONS – FOCUS FOR FUTURE RESEARCH

- FDA data at national US level, and at ex-US level of aggregation. Useful to disaggregate by global region, within the US by state or region, by therapeutic class and route of administration.
- Where is the exit and entry activity of API and FDF manufacturing facilities taking place? What are its causes? Consequences of Puerto Rico hurricane?

Thank you!

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