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The generic drug user fee amendments: an economic perspective

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ABSTRACT

Since the vast majority of prescription drugs consumed by Americans are off patent ('generic'), their regulation and supply is of wide interest. We describe events leading up to the US Congress's 2012 passage of the Generic Drug User Fee Amendments (GDUFA I) as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). Under GDUFA I, generic manufacturers agreed to pay approximately $300 million in fees each year of the five-year program. In exchange, the US Food and Drug Administration (FDA) committed to performance goals. We describe GDUFA I's FDA commitments, provisions, goals, and annual fee structure and compare it to that entailed in the authorization and implementation of GDUFA II on October 1, 2017. We explain how user fees required under GDUFA I erected barriers to entry and created scale and scope economies for incumbent manufacturers. Congress changed user fees under GDUFA II in part to lessen these incentives. In order to initiate and

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sustain user fees under GDUFA legislation, FDA requires the submission of self-reported data on generic manufacturers including domestic and foreign facilities. These data are public and our examination of them provides an unprecedented window into the recent organization of generic drug manufacturers supplying the US market. Our results suggest that generic drug manufacturing is increasingly concentrated and foreign. We discuss the implications of this observed market structure for GDUFA II's implementation among other outcomes.

KEYWORDS: prescription drugs, food and drug administration, regulation, supply, user fees, generic

I. INTRODUCTION

The structure of the industry supplying off patent 'generic' prescription drugs to Americans is of wide interest. The US generic drug industry has grown from modest beginnings into a major component of health care, with generic drugs accounting for the vast majority of retail drug prescriptions dispensed. In 2014, 82% of prescriptions were dispensed at retail as generics, 12% as brands, and 6% as branded generics (those generics marketed with trade names). However, as a share of all retail prescription drug revenues, generics accounted for only 17%, brands 72%, and branded generics 11%.[1]

The market success of generic drugs is in part related to their low cost.[2] On average, oral generics cost 80% less than the brands they replace within five years. Most of the price reductions occur in the first eight months after generic entry.[3] Furthermore, generics commonly capture 80–90% of molecule sales within the year following loss of exclusivity. This is due in part to state mandatory substitution laws, third-party payers and pharmacy benefit managers generously reimbursing pharmacies for dispensing generics over brands, and rewarding prescribers with high rates of generic substitution with bonuses and other incentives. Insured consumers also typically pay lower copayments or coinsurance for generic drugs compared to brand name drugs under tiered formulary arrangements, thereby encouraging them to use generics when available.

As a consequence, many American consumers and policymakers have been surprised by recently reported delayed launches and potentially inadequate supplies of generic drugs that have acted as standard of care for selected diseases, such as the

1 Murray Aitken et al., *Has the Era of Slow Growth for Prescription Drug Spending Ended?*, 35 HEALTH AFF. 1595–603 (2016).

2 U.S. Government Accountability Office, *Drug Pricing: Research on Savings from Generic Drug Use,* GAO-12-371R. Jan. 31, 2012, http://www.gao.gov/assets/590/588064.pdf (accessed Aug. 17, 2017).

3 IMS Institute for Healthcare Informatics, *Price Declines after Branded Medicines Lose Exclusivity in the U.S.*, Jan. 2016, slides 3 and 4, www.theimsinstitute.org (accessed Aug. 10, 2017).

antibiotic doxycycline.[4,5,6] While many of these shortages have resolved, some have persisted over years.[7]

Rising prices among selected generic drugs have also emerged as a concern. Stakeholders have complained of unexpected and unexplained price hikes,[8] prompting investigation by the US Senate Committee on Aging into the practices of 'bad actor' manufacturers.[9] Public outrage regarding large price increases for selected generic drugs has also induced policy makers to take action. The states of Vermont[10] and Maryland[11] have now passed legislation requiring drug price transparency and defined explicit thresholds for identifying drugs exhibiting 'price spikes'. Other agencies are considering similar efforts.

The Generic Drug User Fee Amendments of 2012,[12] commonly referred to as 'GDUFA I', and its reauthorization in Summer 2017, 'GDUFA II', are not the sole factors underlying changes in the structure of the US generic prescription drug industry in the last decade. However, the US Food and Drug Administration (FDA) plays a central role in assuring the accessibility of generic drugs[13] and has increasingly redefined its role to include ensuring competition[14] to promote high-quality manufacturing and constrain high generic drug prices.

Therefore, understanding the details of GDUFA I and II provides an insightful perspective on the regulatory incentives currently faced by generic drug suppliers.

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4 Ed Silverman, *Lawmakers Probe 'Staggering' Price Hikes for Generic Drugs*, The Wall Street Journal, Oct. 2, 2014, http://blogs.wsj.com/pharmalot/2014/10/02/lawmakers-probe-staggering-price-hikes-for-generic-drugs/ (accessed Mar. 6, 2017).

5 U.S. Department of Health and Human Services, Assistant Secretary for Planning and Evaluation (ASPE), *Economic Analysis of the Causes of Drug Shortages*, Issue Brief, Oct. 2011, https://aspe/hhs.gov/pdf-report/economic-analysis-causes-drug-shortages (accessed Mar. 7, 2017).

6 *Prescription Drugs: Comparison of DOD, Medicaid, and Medicare Part D Retail Reimbursement Prices*, GAO-14-578. Washington: DC, June 30, 2014, http://www.gao.gov/products/GAO-14-578 (accessed Aug. 17, 2017) and *Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases*, GAO-16-702. Washington: DC, Aug. 2016. https://www.gao.gov/assets/680/679022.pdf (accessed Aug. 17, 2017).

7 U.S. Government Accounting Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge,* GAO-16-595, Published July 7, 2016, https://www.gao.gov/products/GAO-16-595 (accessed Dec. 6, 2017).

8 Jonathan D. Alpern et al., *High-Cost Generic Drugs—Implications for Patients and Policymakers,* 371 New Eng. J. Med. 1859–62 (2014).

9 U.S. Special Committee on Aging, *Sudden Price Spikes in Off-Patent Prescription Drugs: the Monopoly Business Model That Harms Patients, Taxpayers, and the U.S. Health Care System,* Washington, DC, 2016, http://www.aging.senate.gov/imo/media/doc/Drug%20Pricing%20Report.pdf (accessed Mar. 6, 2017)

10 E. Silverman, *Vermont Becomes First State to Require Drug Makers to Justify Price Hikes,* STAT News, June 6, 2016, https://www.statnews.com/pharmalot/2016/06/06/vermont-drug-prices-transparency/ (accessed Mar. 6, 2017).

11 Jeremy M. Greene & William V. Padula, *Targeting Unconscionable Prescription-Drug Prices—Maryland's Anti–Price-Gouging Law,* New Eng. J. Med., June 7, 2017, http://www.nejm.org/doi/full/10.1056/NEJMp1704907 (accessed Feb. 27, 2018).

12 Public Law 112-144, Title III.

13 Scott Gottlieb M.D, *Antitrust Concerns and the FDA Approval Process*, Statement before the Subcommittee on Regulatory Reform, Commercial and Antitrust Law Committee on the Judiciary United States House of Representatives, July 27, 2017, https://judiciary.house.gov/wp-content/uploads/2017/07/Gottlieb-FDA-Testimony.pdf (accessed Aug. 17, 2017).

14 U.S. FDA, *FDA Tackles Drug Competition to Improve Patient Access: Agency Takes Important Steps Under New Drug Competition Action Plan,* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm564725.htm (accessed Dec. 6, 2017).

We describe events leading up to the 2012 passage of the Generic Drug User Fee Amendments (GDUFA I), and discuss its FDA commitments, provisions, goals, and annual fee structure. We describe the authorization and implementation of GDUFA II in light of GDUFA I's expiration in 2017. These descriptions and their implications for generic drug suppliers by themselves constitute an important contribution to the literature, since we are aware of no published study detailing these regulations and their economic incentives.

In addition, unlike for many other sectors of the US health care system, systematic data on the number, location, and types of firms active in the supply of generic prescription drugs are not the subject of routine reporting by the industry, the press, or government agencies. To implement GDUFA I in fiscal year (FY) 2013, FDA began collecting self-reported information on generic drug manufacturing locations including domestic and foreign active pharmaceutical ingredient (a substance intended to be used as a component of a drug to furnish pharmacological activity—API) and finished dosage form (a drug product in the form in which it will be administered to a patient, such as a tablet, capsule, solution, or topical application—FDF) facilities.[15] To our knowledge, these data have not been analysed and reported publicly in other publications, yet they provide an unprecedented window into the current structure of generic drug manufacturing for the US population. We discuss insights into the current structure of the generic market based on our descriptive analyses of these data.

II. EVENTS LEADING TO GDUFA I: LEGISLATIVE HISTORY, FDA REVIEW COMMITMENTS, AND APPLICATION PROJECTIONS

Over the last few decades, the number of generic drug applications (known as 'Abbreviated New Drug Applications', or 'ANDAs') submitted to FDA for review, and the number of foreign facilities making active pharmaceutical ingredients ('APIs' or drug substance) or finished dosage forms ('FDFs' or 'fill and finish') grew substantially. According to Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research (CDER), by 2010 and 2011, the FDA's generic drug program had become increasingly under-resourced, with its staffing not meeting industry needs, resulting in a growing backlog of submitted but not fully reviewed ANDAs. As observed by Woodcock, the ANDA workload overwhelmed FDA staff and created unpredictability and delay for industry.[16] Moreover, the number of ANDAs submitted to the FDA had mushroomed. Therefore, an urgency emerged in 2011 and 2012 that some type of FDA regulatory overhaul for generic drug oversight and funding was needed. After multiple attempts, FDA and representatives of the generic drug industry developed a proposal for a generic drug user fee program; these proposals were communicated to relevant Senate and House subcommittees overseeing FDA activities in a series of public hearings and private discussions.

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15 U.S. Food and Drug Administration, *Facility Fees,* https://www.fda.gov/forindustry/userfees/genericdruguserfees/ucm319566 (accessed Apr. 5, 2017).

16 Testimony of Janet Woodcock, M.D., *Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA),* Testimony before the Senate Committee on Health, Education, Labor, and Pensions, Jan. 28, 2016, pages 2 and 3 of 20, https://www.fda.gov/newsevents/testimony/ucm484304.htm (accessed Apr. 14, 2017).

Senators Harkin (D-IA) and Enzi (R-WY) were the co-sponsors of Senate bill S. 3187, the 'Food and Drug Administration Safety and Innovation Act' (FDASIA), introduced into the US Congress in May 2012 and signed into law in July 2012 by President Obama.[17] The law amended the Federal Food, Drug, and Cosmetic Act to reauthorize and establish new FDA prescription drug user-fee programs and revise and impose new requirements relating to (1) prescription, pediatric, and generic drugs; (2) medical devices; (3) biosimilar biological products; (4) new infectious disease drugs; and (5) drug manufacturer reporting. GDUFA I is Title III of FDASIA 2012. GDUFA I directed FDA, beginning in FY 2013, to assess and collect fees related to generic drugs (Sec. 302) and required FDA to submit to specific congressional committees annual reports on its progress in achieving GDUFA I's stated goals (Sec. 303). Moreover, FDA was required to submit all applications for approval of a generic drug, amendments to such applications, and prior approval supplements (PAS) with respect to such applications filed in the previous FY (Sec. 308). GDUFA I authorized FDA to appoint employees to perform, administer, or support activities related to the goals of GDUFA (Sec. 307). On October 1, 2017, FDASIA terminated GDUFA I requirements.

According to the Director of the Office of Generic Drugs, at the time of GDUFA I's passage, the three major goals of the legislation were to (i) provide transparency in regulatory policy implementation (achieved through facility identification and improved communications with industry, thereby increasing productivity); (ii) maintain high-quality safety standards, including advancing regulatory science;[18] and (iii) provide predictable and timely access throughout a transparent review process.[19] Moreover, FDA committed it 'will aspire to the extent possible to maintain levels of productivity at least similar to pre-GDUFA levels, while hiring and training incremental staff necessary to achieve the program performance goals, building necessary systems and implementing outlined program changes in years 1 and 2 of the program'.[20]

Under GDUFA I, the generics industry agreed to pay approximately $300 million in fees each year of the five-year program to FDA, adjusted annually for inflation. In exchange, FDA committed to performance goals, the specifics of which were memorialized in the Generic Drug User Fee Act Program Performance Goals and

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17 The Congressional record detailing FDASIA's passage in 2012 may be found here, https://www.congress.gov/bill/112th-congress/senate-bill/3187 (accessed Dec. 5, 2017).

18 Regulatory science issues involving bioequivalence, safety, and efficacy included products with complex active ingredients, inhalation products, abuse-deterrent formulations, complex drug-device combinations, and microspheres (long-acting injectables). See K. Uhl, MD, Director, Office of Generic Drugs (OGD) Director's Update, *Meeting GDUFA Commitments – Going for GOLD*, Powerpoint presentation, GPhA Fall Tech Meeting, Oct. 24, 2016, slide 39 of 84, https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM527918 (accessed Apr. 23, 2017).

19 Kathleen Uhl, M.D., *Office of Generic Drugs (OGD) Director's Update*, Powerpoint slide presentation, GPhA Annual Meeting, Feb. 23, 2016, slides 8–11 of 67, https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeMedicalProductsandTobacco/CDER/UCM487832.pdf (accessed Apr. 21, 2017).

20 Uhl, *supra* note 18, slide 14 of 84 (boldface and underline in original slide footnote) https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM527918 (accessed Feb. 27, 2018).

Procedures document.[21] According to Woodcock, 'Because of the amount of hiring, restructuring, and catch-up needed, performance goals were set to commence in the later years of the program'. GDUFA performance goals with respect to ANDAs, amendments to ANDAs, and PAS[22] are timeframes by which FDA is to take a 'first action' on an application, by either granting an approval or tentative approval,[23] or if there are deficiencies that prevent approval, identifying those deficiencies to the applicant in a complete response letter or in a refusal to receive[24] the application. When deficiencies are identified, industry usually responds by correcting them and resubmitting the application.[25]

Both FDA and the industry believed that in order to achieve these goals, it would initially be necessary for the agency to engage in extensive hiring and training of new personnel; undertake organizational restructuring; implement substantive changes in business processes; and design, create, and implement new information technology platforms and a related informatics infrastructure. However, it was also imperative that the ANDA and PAS backlog of applications be eliminated rapidly. Hence, in GDUFA I, FDA committed to take a first action on 90% of the pre-GDUFA applications pending before the agency on October 1, 2012 by the end of FY 2017. For these reasons, under GDUFA I there were no FDA-specific performance goals for the first two years of the program (ie, FY 2013 and FY 2014). Beginning in FY 2015, a number of performance goals were explicitly agreed to by FDA and the industry.[26] In particular, the pre-GDUFA I applications pending as of October 1, 2012 included 2866 ANDAs and 1873 PASs. As part of GDUFA I, FDA committed to taking a 'first action' on 90% of these 'backlog' applications by the end of FY 2017 (September 30, 2017). In her January 28, 2016 testimony, Woodcock stated that as of December 31, 2015, FDA had completed first actions on 84% of the backlog ANDAs and 88% of the backlog PASs, 'well ahead of schedule in achieving the GDUFA goal to significantly reduce the backlog, and our ultimate goal of eliminating it'.[27]

Some of those backlog applications had been pending or been in review for a long time prior to GDUFA I, due in part to industry's alleged abuse of the citizen

[21] Generic Drug User Fee Act Program Performance Goals and Procedures, https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf (accessed Feb. 28, 2018).

[22] In a footnote in her testimony, Janet Woodcock stated 'A prior approval supplement is a post approval change requiring supplemental submission and approval prior to distribution of the product made using the change' (see note 2 to Jan. 28, 2016 testimony of Director Woodcock cited above).

[23] In a footnote in her testimony, Janet Woodcock went on to state, 'Tentative approval applies if a generic product is otherwise ready for approval before the expiration of any patents or exclusivities accorded to the reference listed drug product. In such instances, FDA issues a tentative approval letter to the applicant. FDA delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product'. (see note 3 to Director Woodcock's Jan. 28, 2016 testimony cited above).

[24] In a footnote in her testimony, Janet Woodcock elaborated, stating 'A 'refuse-to-receive' decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review' (see note 4 to Director Woodcock's Jan. 28, 2016 testimony cited above).

[25] Janet Woodcock January 28, 2016 testimony, op. cit., page 5 of 20.

[26] Testimony of Janet Woodcock, M.D., before the Senate Committee on Health, Education, Labor, and Pensions, Jan. 28, 2016, slides 2 through 9 of 20, https://www.fda.gov/newsevents/testimony/ucm484304.htm (accessed Apr. 14, 2017).

[27] *Id.*

petition process. At the time of Woodcock's January 28, 2016 testimony, 40 months after implementation of GDUFA I on October 1, 2012, each time FDA acted on one of the outstanding backlog applications, the 'time to approval' of such applications was recorded as, at minimum 40 months. Hence, for some time in January 2016 and beyond, over the entire set of submitted ANDAs (both pre-GDUFA I and post-implementation of GDUFA I), the median or mean month approval time was greater than 40 months even though approval times for post-GDUFA I submissions were lower.[28] In addition, Woodcock noted that as of January 28, 2016, the 'filing backlog' for ANDAs, which in August 2014 was over 1100 applications, had been entirely eliminated.[29]

Following implementation of GDUFA I in 2012 and 2013, the number of ANDAs submitted to FDA was much larger than it had experienced in previous years due to the expiration of an unusually large number of 'blockbuster' drugs (the so-called 'patent cliff'). GDUFA I's original review goals, planning, and budgeting were based on the assumption that FDA would receive approximately 750 ANDAs per year. However, according to Woodcock's testimony, in FY 2012, 2013, and 2014 the FDA received 1103, 968, and 1471 applications, respectively, a three-year total of 3542, or 57% more than projected and budgeted.[30] As per the GDUFA I Commitment Letter, these FY 2013 and FY 2014 applications had no GDUFA goal dates. Nonetheless, FDA developed internal goals, called 'Target Action Dates', for both the pre-GDUFA backlog applications and for the FY 2013 and FY 2014 applications, and according to Woodcock's testimony had 'been aggressively reviewing them'.[31] Cumulative hiring for the GDUFA program targeted 231 new reviewers and associated staff employees in FY 2013, 692 new hires by end FY 2014, and 923 new hires by end of FY 2015. Actual hiring of new GDUFA reviewers and associated staff exceeded targets, but not by as much as the increase in ANDA submissions; actual cumulative number of new GDUFA employees was 291 in FY 2013 (26% more than targeted), 882 in FY 2014 (27% more than targeted), and 1192 in FY 2015 (29% more than targeted).[32] Under the GDUFA I agreements, original applications submitted in FY 2015 had a 15-month 'first-action' goal date for 60% of ANDAs, for FY 2016 the GDUFA goal was 75% in 15 months, and for FY 2017 the goal was 90% in 10 months.[33] Moreover, beginning in FY 2015, if the ANDA submission was a potential 'first generic' it automatically received a 15-month

[28] On this, also see, for example, Ed Silverman, *Pharmalot, Is FDA 'Buried' Under a Backlog of Generic Drug Applications?*, Wall Street Journal, July 29, 2014; Tracey Walker, *HSCA to FDA: Address Backlog of Generic Drug Applications*, Formulary Watch, June 9, 2015, http://formularyjournal.modernmedicine.com/formulary-journal/news/hsca-fda-address-backlog-generic-drug-applications (accessed Sept. 12, 2015); Zachary Brennan, *Generic Drug Backlog at FDA: A Dive Into the Confusing Numbers*, Regulatory Affairs Professional Society, Nov. 1, 2016; and Z. Brennan, *FDA Continues to Reduce Generic Drug Backlog*, Regulatory Affairs Professional Society, Feb. 22, 2017.

[29] According to Janet Woodcock's testimony, ' "Filing" is where we evaluate if a drug sponsor's submitted application is sufficiently complete to permit FDA's substantive review'. See page 6 and Chart 6, on page 7 of her 20 page Jan. 28, 2016 testimony.

[30] January 28, 2016 Testimony of CDER Director Woodcock, op. cit., Chart 13 on page 15 of 20. Updated numbers presented by Kathleen Uhl, M.D., Director, Office of Generic Drugs, were 1473 (rather than 1471) for FY 2014, 539 for FY 2015, and 853 (preliminary estimate) for FY 2016. See Uhl, *supra* note 18, slide 12 of 84.

[31] See *supra* note 28.

[32] January 28, 2016 testimony of CDER Director Woodcock, op. cit., Chart 11 on page 13 of 20.

[33] January 28, 2016 testimony of CDER Director Woodcock, op. cit., Chart 4 on page 5 of 20.

goal date. If the ANDA submission could mitigate a drug shortage, its review would also be expedited.

III. GDUFA I: THE CONSTRUCTION OF GENERIC USER FEE SCHEDULES

The GDUFA fee schedule

In order to meet its reviewing commitments on a sustainable basis, FDA needed to collect sufficient user fees to meet its incremental reviewing and inspection workload and costs. This required the agency to make a number of critical decisions as to how fees would be structured under GDUFA I.

At the time it was envisaging a possible GDUFA program in 2011, FDA already had considerable experience with user fees. Since 1992 and the passage of the Prescription Drug User Fee Act ('PDUFA'), FDA had been assessing and collecting fees from sponsors of branded New Drug Applications ('NDAs') and Biologics ('BLAs'), their establishments, and their products.[34] As required by statute, every five years since then the PDUFA program had been reauthorized by Congress.[35] Yet, the inherent nature of regulating generic drugs raised some questions that made the design of GDUFA I different from PDUFA IV, the most proximal legislation ruling branded drug user fees at the time of GDUFA I's passage. A considerable amount has been written about PDUFA in the academic literature, largely focused on the likely intended and unintended impact of user fees on the supply of branded drugs and agency functioning.[36] Here, we briefly describe the PDUFA IV fee structure and compare it to that enacted under GDUFA I, since we are not aware of any previously published papers examining the differences between contemporaneous FDA user fees programs nor their evolution over time.

PDUFA IV, like its predecessors, authorized FDA to collect fees from companies that produce certain branded human drugs and biological products. There were three types of user fees governing these products: 'application fees', establishment fees, and product fees. PDUFA fee revenues collected each year were generated from each of these categories and base revenue amounts derived from PDUFA fees established provisions for FDA workload among other commitments for the upcoming year. While application fees were one-time assessments due at the time of NDAs and BLAs submission, establishment and product fees were assessed annually.

PDUFA defined a prescription drug establishment as 'a foreign or domestic place of business which is at one general physical location consisting of one or more buildings,

[34] More generally, the U.S. Government Accountability Office had issued preliminary guidelines for implementing, funding, and managing user fee programs, which were subsequently finalized in U.S. Government Accountability Office, *Federal User Fees: Fee Design Options and Implications for Managing Revenue Instability*, GAO-13-820, Washington, D.C., Sept. 30, 2013.

[35] The most recent reauthorization of PDUFA occurred in 2017. See for PDUFA VI performance goals: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf (accessed Feb. 27, 2018). Other FDA user fee programs include the Biosimilar User Fee, Medical Device User Fee, Animal Drug User Fee, and the Animal Generic Drug User Fee.

[36] Please see, for example, Deborah G. Parver, *Expediting The Drug Approval Process: An Analysis of the FDA Modernization Act of 1997*, 51 ADMIN. L. REV. 1249–66(1999); Peter B. Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431–86 (2008); Tomas J. Philipson & Eric Sun, *Is the Food and Drug Administration Safe and Effective?*, 22 J. ECON. PERSP. 85–102 (2008); and Henry Grabowski & Richard Y. Wang, *Do Faster Food and Drug Administration Drug Reviews Adversely Affect Patient Safety? An Analysis of the 1992 Prescription Drug User Fee Act*, 51 J. L. & Econ. 377–406 (2008).

Table 1. PDUFA Fee Schedule for FY 2011.

Applications	
Requiring clinical data	$1542,000
Not requiring clinical data	$771,000
Supplements requiring clinical data	$771,000
Establishments	$497,200
Products	$86,520

Source: Department of Health and Human Services, U.S. Food and Drug Administration, Prescription Drug User Fee Rates for FY 2011', Docket No. FDA-2010-N-0390, Notice, Federal Register Volume 75, Number 149, pages 46,952-46,957, August 4, 2010, https://www.gpo.gov/fdsys/pkg/FR-2010-08-04/html/2010-19116.htm (accessed Apr. 16, 2017).

all of which are within five miles of each other, and at which one or more prescription drug products are manufactured in final dosage form. For purposes of user fees, the term manufactured does not include packaging.…Final dosage form means a finished dosage form which is approved for administration to a patient without substantial further manufacturing'.[37,38]

For FY 2011, total PDUFA user fee revenues were set at $619,070,000, allocated one third each to application, establishment, and product fees. To transform this into per application, per establishment, and per product user fees, FDA needed to collect data enabling it to estimate numbers for each of these three categories. Data gathered from implementation of Section 510 of the *Federal Food, Drug and Cosmetic Act* mandated that 'firms that manufacture, prepare, propagate, compound or process drugs in the U.S. or that are offered for import into the U.S.' to register with the FDA. These domestic and foreign firms must, at the time of registration, list all drugs manufactured, prepared, propagated, compounded, or processed for commercial distribution in the US. Additionally, foreign establishments must identify a US agent and importer at the time of registration.[39] These registration requirements enabled FDA to estimate the number of establishments and number of products and verify their identities.

Having obtained estimates of these various workload metrics for FY 2011 in July 2010 FDA announced the schedule of PDUFA user fees for FY 2011 (Table 1).[40] NDAs

[37] U.S. Food and Drug Administration, *Frequently Asked Questions on Prescription Drug User Fees (PDUFA)*, CDER Small Business and Industry Assistance, not dated, page 3 of 12, https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069943.htm (accessed Apr. 16, 2017).

[38] Several waivers were available for the user fees, eg, for orphan drugs and small businesses submitting their first human drug application, for establishments listed in the human drug application that do not engage in the manufacture of the prescription drug product during the year, for products whose NDA/BLA was approved before Oct. 1, 1992, and for products whose ANDA was approved before or after the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984. See *Id.* at 4–6 of 12.

[39] U.S. Food and Drug Administration, *Drug Registration and Listing System (DRLS and eDRLS)*, not dated but after Aug. 2016, page 1 of 3, https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm (accessed Apr. 16, 2017).

[40] In FY 2011, there were 117.5 Full Application Equivalents, 415 fee-paying establishments, and 2,385 products. For details, see Department of Health and Human Services, U.S. Food and

and BLAs generally require clinical data, but PAS applications for a previously approved NDA or BLA may not require FDA evaluation of additional clinical data. To the extent an establishment manufactured multiple FDF products for it and its affiliates, or as a contract manufacturer for other marketed drugs, the establishment fee could be shared across products and/or firms.

Although FDA's experience with the PDUFA user fee program for NDAs and BLAs provided it with valuable insights in designing and implementing a GDUFA program for generic drugs, some key features of the products were different. While PDUFA was concerned with costs associated with FDA reviewing clinical data on novel molecules and on monitoring the marketing and advertising of branded drugs in various media, GDUFA involved a more intense focus by the agency on manufacturing and bioequivalence issues.[41,42]

How FDA and the industry would design a GDUFA inspection program and associated user fee schedule to meet two other new challenges was becoming a highly visible issue by 2011.[43] First, evidence was emerging that the outsourcing of manufacturing of API and FDF to contract manufacturers had more than doubled between 2001 and 2010, with much of the contract manufacturing now being outsourced to off-shore entities, particularly to India, China, and Eastern Europe. While off-shoring to contract manufacturing was occurring for both brands and generics, the outsourcing was apparently greater for generics than brands. Notably, prior to GDUFA, FDA was required to inspect domestic human generic drug manufacturers every two years, but no such requirement existed for foreign manufacturers. This disparity between domestic and foreign manufacturing inspection requirements, combined with insufficient resources, created significant vulnerabilities in the global prescription drug supply chain. To promote inspection parity between domestic and foreign facilities, it was recognized that FDA would need resources to maintain the same high-quality standards.[44]

Second, as far back as 2007 public attention was focusing on adulterated food manufactured in China. In particular, the industrial poison melamine was found in pet food that sickened and killed hundreds of US cats and dogs; melamine was later found in dairy products, including baby formula, blamed for sickening thousands of infants and

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Drug Administration, Prescription Drug User Fee Rates for FY 2011, Docket No. FDA-2010-N-0390, Notice, Federal Register, Volume 75, No. 149, pages 46952–46957, Aug. 4, 2010, https://www.gpo.gov/fdsys/pkg/FR-2010-08-04/html/2010-19116.htm (accessed Apr. 16, 2017).

41 The extent of nonprice competition depends in large part on how nonprice features (eg, quality and reliability of supply) is observable. For generic drugs, observability of such nonprice features may be very limited. On this, see Janet Woodcock & Marta Wosinska, *Economic and Technological Drivers of Sterile Injectable Drug Shortages*, 93 CLIN. PHARMACOL. & THER. 170–76 (2013), http://www.nature.com/clpt/journal/v93/n2/full/clpt2012220a.html (accessed Aug. 10, 2017).

42 Some postapproval drug safety activities are equally relevant for generic drugs as they are for branded drugs (eg, Risk Evaluation and Mitigation Strategies (REMS) and REMS compliance, adverse event reporting and surveillance, including through Sentinel; and current Good Manufacturing Practices (cGMP) monitoring).

43 For a more recent updated discussion of attempts by industry, academia, and the FDA to prevent heparin manufacturing fraud, see Jean-François Tremblay, *Making Heparin Safe,* 94 CHEM. & ENG. 30–4 (2016), http://cen.acs.org/articles/94/i40/Making-heparin-safe.html (accessed Apr. 17, 2017).

44 U.S. Food and Drug Administration, *GDUFA Performance Reports*, not dated, page 1 of 2, https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/default.htm (accessed Aug. 17, 2017).

killing four.[45] Then, in April 2008, FDA released a report claiming that at least 81 deaths and 785 reports of serious injuries were believed to be linked to a raw heparin ingredient imported from China.[46] Working with the involved pharmaceutical companies and academics, FDA identified the contaminant in heparin as an 'oversulfated' derivative of chondroitin sulfate. Since oversulfated chondroitin is not a naturally occurring molecule, costs a fraction of true heparin starting material (typically from the mucosa of pigs' intestines), and mimics the in vitro properties of heparin, FDA surmised the counterfeit was almost certainly intentional. Under intense questioning from congressional investigators inquiring why the adulterations had not been uncovered by inspections of foreign API manufacturing facilities, FDA officials admitted they had mistakenly failed to conduct an inspection of the ultimately identified Changzhou SPL plant, but said that an inspection would not have been able to uncover the contaminations.[47] According to the *New York Times*, FDA CDER Director Woodcock testified that FDA would need another $225 million annually to inspect every foreign drug plant every other year, the frequency many said was needed. She also noted the agency would be spending $11 million on foreign drug inspections in FY 2008. According to the *New York Times* journalist covering the hearing, '…there is growing bipartisan consensus on Capitol Hill that the FDA needs a rapid increase in its budget to ensure the safety of the nation's drugs, medical devices and food'.[48]

As a result, although FDA's preparation for GDUFA I in 2011 and 2012 overlapped in time with its preparation for reauthorization of PDUFA V (required by October 1, 2012), the two user fee programs were viewed by the agency as different in focus and goals. In particular, documents summarizing PDUFA V reauthorization performance goals and procedures for FYs 2013 through 2017 made no mention of distinguishing between foreign and domestic new on-patent drug and biologic applications and Investigational NDAs. While there was some discussion in the planning documents of original manufacturing supplements, no distinction was made between foreign and domestic manufacturing sites, API vs. FDF facilities, nor the geographical focus and intensity of manufacturing facilities, and no mention was made of contract manufacturing, outsourcing, or Drug Master Files (DMFs).[49] When PDUFA V Drug User Fee rates for FY 2013 were announced in August 2012, their structure (but not amounts) was virtually identical to that for FY 2011, and consisted of one-time application fees, and annual establishment and product fees, with no

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45 Larry Greenemeier, *Heparin Scare: Deaths from Tainted Blood-Thinner Spur Race for Safe Replacement*, Scientific American, Nov. 4, 2008, https://www.scientificamerican.com/article/heparin-scare-deaths/ (accessed Apr. 17, 2017).

46 Wikipedia, *2008 Chinese Heparin Adulteration,* https://en.wikipedia.org/wiki/2008_Chinese_heparin_adulteration (accessed Apr. 17, 2017).

47 *The Heparin Disaster: Chinese Counterfeits and American Failures,* Hearing Before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, House of Representatives, Apr. 29, 2008, https://www.gpo.gov/fdsys/pkg/CHRG-110hhrg53183/html/CHRG-110hhrg53183.htm (accessed Aug. 18, 2017).

48 Gardiner Harris, *Heparin Contamination May Have Been Deliberate, F.D.A. Says*, New York Times, Apr. 30, 2008, http://www.nytimes.com/2008/04/30/health/policy/30heparin.html (accessed Apr. 17, 2017).

49 See, for example, *PDUFA V Reauthorization Performance Goals and Procedures: FYs 2013 through 2017*, PDF – 130KB, https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf (accessed Apr. 17, 2017). We discuss DMFs in greater detail later in this paper.

differentiation among foreign and domestic applications.[50] Hence, while manufacturing issues for pharmaceuticals were very much in the news in 2011, apparently they were not perceived as being related to reviewing and monitoring branded NDAs or BLAs, but rather were confined to generic drugs and ANDAs.

Generic manufacturing data needed to calculate user fees and to portray current structure of the generic industry

Although over the years FDA had gathered and curated data from branded drug sponsors of new on-patent drugs and biologics enabling them to design user fee schedules to cover PDUFA costs, this was not the case for generic manufacturers and ANDA holders. Given the heterogeneity in how and where ANDA holders manufactured generic drugs (eg, in-house for both API and FDF, at facility site same as or different from headquarters, in-house FDF but outsourced API, outsourced both API and FDF, and not an ANDA holder but instead just a contract manufacturer to other firms who were ANDA holders), and given the increased outsourcing to off-shore entities, it was clear the FDA needed to gather accurate and up-to-date data on the activities of ANDA holders and detailed information on how their manufacturing operations were organized, and if not an ANDA holder, how contract manufacturing operations were structured.

To obtain this detailed information, GDUFA I explicitly mandated that human generic drug facilities, and certain sites and organizations identified in a generic drug submission, provide identification information to the FDA annually between May 1 and June 1 to 'self-identify themselves'.[51] According to the legislation, 'This information will assist in constructing an accurate inventory of facilities, sites and organizations involved in the manufacture of generic drugs, setting annual facility fee amounts, and targeting inspections'.[52] Self-identification was required for two purposes. First, it was necessary to determine the universe of facilities required to pay user fees. Second, self-identification was a central component of an effort to promote global supply chain transparency. According to FDA, the information provided through self-identification would enable quick, accurate, and reliable surveillance of generic drugs and facility inspections and compliance.[53]

If facilities were to be assessed user fees and be targets of inspections, it would be necessary first to define what is a facility. According to the GDUFA I legislation:

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[50] In particular, application fees requiring clinical data were $1,958,800, not requiring clinical data $979,400, and supplements requiring clinical data $979,400, while establishment fees were $526,500 and product fees $98,380. See Department of Health and Human Services, U.S. Food and Drug Administration, *Prescription Drug User Fee Rates for Fiscal Year 2013,* Docket No. FDA 2012 N 007, Notice, Federal Register Volume 77, Number 148, pages 45639–45643, https://www.federalregister.gov/documents/2012/08/01/2012-18711/prescription-drug-user-fee-rates-for-fiscal-year-2013 (accessed Feb. 28, 2018).

[51] Daniel Henrich, *GDUFA and Self-Identification: What's changing? (And What's Not?),* KNOWLEDGE.REEDTECH, Feb. 9, 2017, page 1 of 3, http://knowledge.reedtech.com/life-sciences-all-posts/gdufa-what-is-changing (accessed Apr. 6, 2017).

[52] U.S. Food and Drug Administration, *Self-Identification FAQs*, not dated, https://www.fda.gov/forindustry/userfees/genericdruguserfees/ucm320942.htm (accessed Apr. 14, 2017).

[53] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, *Self-Identification of Generic Drug Facilities, Sites and Organizations: Guidance for Industry*, Sept. 2016, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (accessed Apr. 14, 2017).

> GDUFA defines a facility as a business or other entity under one management, either direct or indirect, at one geographic location or address, engaged in manufacturing or processing an API or an FDF. It does not include a business or other entity whose only manufacturing or processing activities are one or more of the following: repackaging, relabeling, or testing. Separate buildings within close proximity are considered to be at one geographic location or address if the activities in them are closely related to the same business enterprise; are under the supervision of the same local management; and are capable of being inspected by FDA during a single inspection.[54]

The GDUFA legislation required the following types of generic industry facilities, sites, and organizations to self-identify with FDA annually:[55]

1. Facilities that manufacture, or intend to manufacture, human generic drugs, APIs, or both.[56]
2. Sites and organizations that package the FDF of a human generic drug into the primary container/closure system and label the primary container/closure system.[57]
3. Sites that are identified in a generic drug submission and pursuant to a contract with the applicant remove the drug from a primary container/closure system and subdivide the contents into a different primary container/closure system.
4. Bioequivalence (BE)/bioavailability (BA) sites that are identified in a generic drug submission and conduct clinical BE/BA testing, bioanalytical testing of samples collected from clinical BE/BA testing, and/or in vitro BE testing.
5. Sites that are identified in a generic drug submission and perform testing of one or more attributes or characteristics of the FDF or the API pursuant to a contract with the applicant to satisfy a cGMP testing requirement (excludes sites that are testing for research purposes only).[58]

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54 U.S. Food and Drug Administration, *supra* note 53, not dated, page 1 of 4.

55 *Id.*

56 The following text was included in a note at this location on page 2 of the original 'Self-Identification FAQs' document referenced above: 'For purposes of self-identification and payment of fees, GDUFA defines API and FDF manufacturers differently from the way these categories of manufacturers have been defined historically. For example, generic drug manufacturers who mix an API when the substance is unstable or cannot be transported on its own are considered API manufacturers and not FDF manufacturers for self-identification and the payment of GDUFA fees only. GDUFA defines an FDF as: (A) a drug product in the form in which it will be administered to a bpatient, such as a tablet, capsule, solution, or topical application; (B) a drug product in a form in which reconstitution is necessary prior to administration to a patient, such as oral suspensions or lyophilized powders; or (C) any combination of an active pharmaceutical ingredient (as defined in the statute) with another component of a drug product for purposes of production of a drug product described in subparagraph (A) or (B). GDUFA defines an API as: (A) a substance, or a mixture when the substance is unstable or cannot be transported on its own, intended – (i) to be used as a component of a drug; and (ii) to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or (B) a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become a substance or mixture described in subparagraph (A)'.

57 The following text was included in a note at this location on page 2 of the original 'Self-Identification FAQs' document referenced above: 'Sites and organizations that package the FDF of a human generic drug into the primary container/closure system and label the primary container/closure system are considered to be manufacturers, whether or not that packaging is done pursuant to a contract or by the applicant itself'.

58 U.S. Food and Drug Administration, *supra* note 53, not dated, pages 2 and 3 of 4.

To encourage full participation in the self-identification process, FDA announced that not all facilities, sites and organization that must self-identify would be assessed user fees. Only facilities that manufacture, or intend to manufacture, generic drug APIs or FDFs, or both, would be required to pay facility fees. Sites and organizations that only performed testing, repackaging, or relabeling would not be required to pay a user fee. Moreover, no facility would be required to pay more than one annual FDF fee and/or one annual API fee, if applicable. Regarding a penalty for those failing to self-identify, FDA announced that:

> Under GDUFA, if a facility fails to self-identify, all FDF or API products manufactured at the facility and all FDFs containing APIs manufactured at the facility will be deemed misbranded. It is a violation of federal law to ship misbranded products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of the misbranded products. Products that are deemed misbranded because of failure of the facility to self-identify are subject to being denied entry into the United States.[59]

According to FDA, across the five-year initial reporting period, an average of 3500 GDUFA facilities, sites, and organizations self-identified each FY.[60] Each year 60 days before the beginning of the following FY, FDA announces generic drug user fee rates for the upcoming year and publishes them in the *Federal Register*. As part of that announcement, FDA also provides counts of API and FDF facilities, domestic and foreign, that provide the basis for calculation of the per API and per FDF facility fees.

In Table 2, we reproduce facility counts for FYs 2013 through 2017 obtained from the generic drug manufacturers' self-identification process.[61] It is instructive to observe the composition and trends in the geographic locations of FDF and API facilities. For example, looking at the last three columns, we observe that globally the total number of FDF plus API facilities ('ALL') fell about 11%, but the decline in domestic facilities at 20% (third last column) was almost three times that for foreign facilities (second last column), that had a decline of just over 7%. Moreover, the proportional domestic/foreign decline in the total number of facilities varied depending on whether it is FDF or API facilities. While the percent decline for domestic facilities was roughly 21–22% for both FDF and API facilities, there was about a 10% decline in foreign API facilities and only a 3% decline in foreign FDF facilities. Thus, between 2013 and 2017, the US shed about 21–22% of both FDF and API facilities, while the number of foreign API facilities fell about half that much (about 10%), and the number of foreign FDF

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59 *Id*, not dated, page 4 of 4.

60 The number self-identifying was 3,334 (FY 2013), 3,604 (FY 2014), 3,335 (FY 2015), 3,641 (FY 2016), and 3,605 (FY 2017). See U.S. Food and Drug Administration, *FY 2016 Performance Report to Congress for the Generic Drug User Fee Amendments*, page 11 of 26 plus three appendices, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM541886.pdf (accessed Apr. 24, 2017).

61 For FY 2013, see https://www.gpo.gov/fdsys/pkg/FR-2012-10-25/pdf/2012-26256.pdf; for FY 2014, see https://www.gpo.gov/fdsys/pkg/FR-2013-08-02/pdf/2013-18625.pdf; for FY 2015, see https://www.gpo.gov/fdsys/pkg/FR-2014-08-01/pdf/2014-18108.pdf; for FY 2016, see https://www.gpo.gov/fdsys/pkg/FR-2015-08-03/pdf/2015-18915.pdf; and for FY 2017, see https://www.gpo.gov/fdsys/pkg/FR-2016-07-27/pdf/2016-17801.pdf. All documents (accessed Apr. 18, 2017).

Table 2. Generic Manufacture Facility Counts and Location from Annual Self Identification Responses.

	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	87.3	1464	356	1108	75.7
MEAN	290	424	59.5	114	728	86.7	1555	404	1151	74

Source: Authors' calculations from the following data files: For FY 2013, see https://www.gpo.gov/fdsys/pkg/FR-2012-10-25/pdf/2012-26256.pdf; for FY 2014, see https://www.gpo.gov/fdsys/pkg/FR-2013-08-02/pdf/2013-18625.pdf; for FY 2015, see https://www.gpo.gov/fdsys/pkg/FR-2014-08-01/pdf/2014-18108.pdf; for FY 2016, see https://www.gpo.gov/fdsys/pkg/FR-2015-08-03/pdf/2015-18915.pdf; and for FY 2017, see https://www.gpo.gov/fdsys/pkg/FR-2016-07-27/pdf/2016-17801.pdf (accessed Apr. 18, 2017).

facilities fell only slightly, about 3%. Hence, for both FDF and API manufacturing, facilities are not only predominantly foreign, but are generally increasingly foreign over time.

Moreover, while on average about 60% of FDF facility sites are foreign, almost seven out of every eight API facility sites are foreign, and for both FDF and API the share foreign has generally been increasing between 2013 and 2017. Therefore, although in terms of sales revenues generated, the US generic prescription drug industry may be the largest national market globally, and the US generic drug manufacturing sector is rather modest in size with the vast majority of generic prescription drugs sold to Americans being manufactured abroad. An implication is that FDA regulation of generic manufacturing facilities is primarily an off-shore effort, likely requires foreign and technical language proficiency, and is more focused on API than FDF facilities. Whether these geographical shares and trends are similar for branded drugs is unknown.

From another perspective, these data suggest that although the total number of FDF (Table 2, column 2 plus column 3) and the total number of API facilities (Table 2, column 5 plus column 6) manufacturing drugs approved for sale in the US have each declined by 10–11% between 2013 and 2017, the geographic composition change has been quite dramatic—with a greater decline in domestic FDF facilities (column 2) than in domestic API facilities (column 5), but with the number of domestic FDF facilities (column 2) still about two and one-half times larger than the number of domestic API facilities (column 5). These trends suggest that the location and type of facility inspections carried out by FDA are increasingly global operations, and increasingly involve API rather than FDF inspections. Domestic generic manufacturing includes primarily FDF rather than API activities.

The composition of generic user fees

Components of the GDUFA fee structure include a one-time ANDA fee, a one-time PAS fee for each supplement to an ANDA—both of which are due on the date of submission, a one-time DMF due no later than the date on which the first ANDA submission is submitted that references the associated DMF, and annual API and FDF facility fees.

Regarding PASs for approved ANDAs, FDA regulations in 21 CFR 314.70 distinguish major manufacturing changes, moderate manufacturing changes, and minor manufacturing changes. A major change 'has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a PAS and approval by FDA before distribution of the drug product made using the change'.[62] In contrast, a minor change is 'a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the

[62] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, *ANDA Submissions—Prior Approval Supplements Under GDUFA: Guidance for Industry*, Oct. 2016, page 4 of 14, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (accessed Apr. 19, 2017).

drug product. The applicant must describe minor changes in its next annual report'.[63] In between major changes and minor changes are moderate changes—'a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. Depending on the nature of the change, one of the following two types of supplements must be submitted to FDA for a moderate change:[64] a Changes Being Effected in 30 Days (CBE-30) supplement that requires submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change; and a Changes Being Effected supplement involving certain moderate changes that allows distribution to occur as soon as FDA receives the supplement (CBE-0)'. FDA has discretion regarding whether a PAS requires an inspection. Note that only major changes require submission of a PAS, moderate changes can be addressed with CBE supplements and minor changes can be communicated in the company annual report to FDA.[65] User fees are required for all PASs, including labeling and microbiology as well as change in API or FDF manufacturer that require prior approval under FDA regulations. If FDA determines that the proposed manufacturing change to an approved product was submitted incorrectly as a CBE, FDA notifies the applicant that the proposed change must be considered a PAS. The applicant must resubmit the change as a PAS along with payment of a PAS fee. The GDUFA regulations did not change the criteria in PDUFA for when a particular category of supplement (PAS, CBE-0, CBE-30) must be submitted.[66] Note also that under PDUFA if an establishment ceases production of FDFs of all its NDAs/BLAs for an entire year, its annual establishment fee is waived. However, if a facility manufacturing approved ANDAs ceases manufacturing all its ANDAs at that site for an entire year, under GDUFA I that facility is still assessed an annual facility fee.

One other important document review subject to a one-time GDUFA user fees is the DMF, a confidential detailed document submitted by API and FDF manufacturers to FDA. A DMF contains information regarding the chemistry, manufacturing, and controls of a drug component. There are five types of DMFs; type II is the most common type for an ANDA applicant.[67] It is a submission of information to FDA to permit the agency to review the information in support of a third party's submission without revealing the information to the third party.[68] Components of a drug include the API or drug substance, excipients, and packaging material. There is no legal or regulatory requirement to file a DMF. Information usually contained in a DMF can

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63 U.S. Food and Drug Administration, *Abbreviated New Drug Application (ANDA) and Prior Approval Supplement (PAS) Fees,* not dated, page 3 of 4, https://www.fda.gov/ForIndustry/UserFees/ucm319568.htm (accessed Apr. 19, 2017).

64 *Id.*

65 *Id.* pages 5–7 of 14.

66 U.S. Food and Drug Administration, *supra* note 64, not dated, page 3 of 4.

67 Kathlyn Stone, *Drug Master File: What Is This Detailed Document?,* The Balance, updated Oct. 13, 2016, page 1 of 3, https://www.thebalance.com/drug-master-file-dmf-2663082. (accessed Feb. 28, 2018).

68 The information presented in the remainder of this paragraph is taken in large part from a 44-slide Powerpoint presentation by Arthur B. Shaw, Ph.D., FDA DMF Expert, FDA Small Business Office Webinar, Feb. 11, 2013, *Drug Master Files Under GDUFA: DMF Basics*, https://www.fda.gov/downloads/drugs/developmentapprovalprocess/.../ucm339118. https://www.fda.gov/downloads/drugs/developmentapprovalprocess/.../ucm339118 (accessed Aug. 10, 2017).

instead be provided in an NDA or ANDA. ANDA applicants who intend to outsource API manufacturing can reference a DMF held by another entity. FDA maintains a DMF website[69] that contains a current list of DMFs and their holders, but maintains confidentiality of its proprietary information, such as manufacturing procedures for the DMF holder. The existence of a DMF permits review of information by reviewers at FDA to support ANDA applications submitted by one or more applicants. If a number of ANDA applicants seek to outsource their API manufacturing of the same molecule/formulation/strength API to a common contract manufacturing organization (so-called 'CMO') that is a DMF holder, each of the ANDA applicants can reference the same DMF in its ANDA application; it is also possible for one DMF holder to reference another DMF holder. Although FDA maintains confidentiality of the DMF contents, the DMF holder and its ANDA holder clients can reach their own agreements concerning information sharing.

As part of an ANDA, the applicant encloses a letter of authorization from the DMF holder, granting FDA authorization to review the DMF, and granting the authorized party, i.e., the ANDA applicant, the right to incorporate the information in the DMF by reference.[70] DMFs are neither approved nor disapproved; rather, a DMF is reviewed to determine whether it is complete and adequate to support the particular application that references it.[71] When authorized parties or DMF holders have a name change, they must notify FDA; FDA recommends that the DMF holder notify all authorized parties of a name change. If a DMF holder withdraws authorization for a customer to reference the DMF, this is submitted to FDA as a 'Withdrawal of Authorization' document.[72]

Under GDUFA I, the DMF user fee is triggered when the DMF reference is included in the original ANDA submission, an amendment to an ANDA, a PAS, and an amendment to a PAS, but the user fee is not triggered by CBE-0 or CBE-30 supplements. The DMF fee is a fee paid only once during the DMF lifecycle,[73] but who pays the DMF fee is unspecified. In particular, if a DMF holder is only a contract manufacturer and does not hold any NDAs or ANDAs, but sells API or FDF to the NDA or ANDA holder, then the DMF holder likely pays the one-time DMF user fee, prior to it being referenced by the NDA or ANDA holder. On the other hand, if an ANDA applicant intends to reference a DMF in its application, and if no other ANDA, NDA, or DMF holder has referenced that DMF holder, then who pays the DMF user fee is negotiated between the ANDA applicant and the DMF holder.

Following passage of GDUFA I, a number of CMOs who were not ANDA holders and instead simply served as back-up sources to ANDA holders seeking to ensure themselves against manufacturing disruptions, voiced concerns that the existence of the

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69 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm (accessed Aug. 10, 2017).

70 Arthur B. Shaw, *supra* note 69, slides 15 and 19 of 44.

71 *Id*. slide 31 and 39 of 44.

72 *Id*. slide 20 of 89.

73 David Skanchy, Ph.D., Director, DMF Review Staff, Office of Generic Drugs, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Small Business Webinar on DMFs under GDUFA, Feb. 11, 2003, powerpoint slide presentation, '*New DMF Requirements Based on GDUFA*' slides 47 and 48 off 66, https://www.fda.gov/downloads/drugs/developmentapprovalprocess/.../ucm339118.https://www.fda.gov/downloads/drugs/developmentapprovalprocess/.../ucm339118 (accessed Aug. 10, 2017).

DMF fee and how it was being assessed could encourage exit by small businesses, although others noted that since many DMF holders were foreign small businesses with limited and infrequent production runs, the DMF fee might induce them to exit and thereby benefit domestic DMF small businesses.[74]

In order to arrive at a per initial DMF user fee assessment, FDA needed to estimate the number of initial letters of reference to a DMF for each forthcoming FY. For FY 2013, that number was estimated as 700; for FY 2014, it was 583; for FY 2015, 701; for 2016, 453; and for FY 2017, 369.[75] Why the number of DMF reference letters has declined by almost 50% since 2013 is unclear, but it could reflect exit and less entry by small CMOs, particularly from emerging economies, for whom it would be a significant barrier to entry. This issue is worthy of further research.

Having estimated the number of FDF and API facilities, foreign and domestic, as well as number of likely ANDA, PAS, and DMF applications, along with the agency's incremental costs associated with the GDUFA program, FDA and the industry needed to allocate fees to one-time application fees and annual user fees. Negotiations yielded an allocation of 30% of total GDUFA fees to one-time user fees (24% for ANDAs and 6% for DMFs), and 70% to annual GDUFA program fees (split 14% to API facilities and 56% to FDF facilities).

The resulting GDUFA I user fee schedule, for each FY between 2013 and 2017, is reproduced in Table 3.[76]

Several entries in Table 3 merit comment. First, in terms of sheer dollar magnitude, the FDF-D and FDF-F annual user fees at greater than $200,000 are by far the largest user fee component, followed by one-time ANDA fees that ranged from $50K to $70K between 2013 and 2017. Second, while in 2013, at about $21K the smallest user fee was for DMFs, by 2017 the PAS fees at $35K were the smallest. Third, in all years the foreign-domestic FDF and API facility fee differential was $15K. Fourth, API facility fees were only a fraction of FDF facility fees, which for domestic facilities ranged from about 15% in 2013 to 17% in 2017. Notably, if a facility manufactures both generic FDFs and APIs, under GDUFA I such a facility incurs both annual FDF and annual API facility fees.[77] Finally, although annual user fee changes were mostly positive, in some cases they were negative; over the entire 2013–2017 period, all GDUFA I user fee types had substantially positive compound annual growth rates (CAGRs). At 24%, the 2013–2017 CAGR for DMFs was the largest, followed by about 10–14% for the annual API and FDF domestic and foreign facility fees, and just above 8% for the ANDA and PAS one-time submission fees.

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74 See, for example, Steven Pressman, *How Will GDUFA Impact Contract Manufacturers and Packagers?*, Pharma & Biopharma Outsourcing Association, Sept. 26, 2012, http://www.pharma-bio.org/blog/how-will-gdufa-impact-contract-manufacturers-and-packagers/ (accessed Aug. 3, 2015;); Gil Y. Roth, *Generic Manufacturing: GDUFA & CMOs,* Contract Pharma, Mar. 6, 2013, http://www.contractpharma.com/issues/2013-03/view_features/generic-manufacturing-gdufa, (accessed Aug. 3, 2015); and Glessner, *supra* note 44.

75 See *supra* note 62.

76 *Id.*

77 U.S. Food and Drug Administration, *Generic Drug User Fee Amendments of 2012: Facility Fees*, not dated, page 2 of 3, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm316671.pdf (accessed Feb. 28, 2018).

Table 3. 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%	24.2%	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.

Source: Authors' calculations from the following data files: For FY 2013, see https://www.gpo.gov/fdsys/pkg/FR-2012-10-25/pdf/2012-26256.pdf; for FY 2014, see https://www.gpo.gov/fdsys/pkg/FR-2013-08-02/pdf/2013-18625.pdf; for FY 2015, see https://www.gpo.gov/fdsys/pkg/FR-2014-08-01/pdf/2014-18108.pdf; for FY 2016, see hhttps://www.gpo.gov/fdsys/pkg/FR-2015-08-03/pdf/2015-18915.pdf; and for FY 2017, see https://www.gpo.gov/fdsys/pkg/FR-2016-07-27/pdf/2016-17801.pdf (accessed Apr. 18, 2017).

Implications of generic user fees for generic drug manufacturers

GDUFA fee structures have some interesting implications for generic drug manufacturers, most easily appreciated by comparing to that implied by the PDUFA user fees discussed above. First, since there is at most only one establishment fee at each establishment, with PDUFA economies of scope can be exploited by locating the FDF manufacturing of multiple products at the same establishment, thereby avoiding multiple annual establishment fees. However, for a drug developer having no approved products, or having an approved NDA but not manufacturing the FDF of that product in house, the annual establishment fee can be avoided by outsourcing the FDF to a CMO, who would need to pay an annual FDF fee, and perhaps earlier have paid a one-time DMF fee. There is also an incentive for the manufacturer of the new on-patent drug or biologic application holder to vertically integrate, in that a branded firm with an NDA can outsource FDF and API manufacturing to its generic subsidiary, who simultaneously can serve as a CMO to ANDA holders while holding the single DMF, paying annual API and FDF fees that are considerably less than annual establishment fees.

However, for ANDA holders the incentives to outsource might be even greater, particularly for new ANDA holders not having in-house API or FDF facilities. By outsourcing, ANDA holders can avoid the annual API and FDF facility fees. For ANDA holders already having multiple API and FDF facilities, there are incentives to become a CMO for other ANDA holders, since as long as the existing API and FDF facilities could manufacture additional products they would not be assessed additional annual facility fees and thereby enjoy scope economies. In turn, for the CMO there are economies of scale in that a single DMF holder serving as a CMO making the same API or FDF product for several ANDA holders pays only one annual API or FDF fee, all made possible by having previously paid a single DMF fee. This incentive for CMOs to manufacture

the same API or FDF product for different applicants can lead to highly concentrated manufacturing of a product, making that product susceptible to supply disruptions and possibly leading to shortages and price increases. It is important that recent events regarding shortages of off-patent generic drugs, and of price increases involving them, be considered in this context.[78]

Moreover, from the GDUFA I fee structure the locus of API and FDF manufacturing can become quite complicated for ANDAs, both in terms of organizational structure and logistics. Since GDUFA I is structured to facilitate the possible reduction of establishment and facility fees for a single firm having both branded NDA and generic ANDA divisions, strategic consolidation issues concerning governance and corporate affiliation may also emerge.

Finally, it is worth noting that the GDUFA I fee structure increases the carrying costs to an ANDA holder for temporarily discontinuing production and marketing of a product. Instead of permanently withdrawing and rescinding an ANDA, an ANDA holder can inform the FDA it is temporarily discontinuing the marketing of a product.[79] Even if it involved closing an entire FDF or API manufacturing facility, under GDUFA I the ANDA holder is assessed annual API and FDF facility fees during the duration of the temporary discontinuation period. In this way, the facility fee assessment encourages firms to withdraw and completely rescind their ANDA asset, rather than temporarily hibernating it for possible subsequent re-entry. Whether the FDA will require facility inspection, or submission of a PAS, before resumption of production is approved by the FDA, depends on a number of matters that are negotiated between the FDA and the ANDA holder.[80]

IV. EVALUATIONS AND CRITIQUES OF GDUFA I: WHAT WAS AND WHAT NEEDS TO BE LEARNED?

FDA's authorization and reauthorization processes for its user fee programs are somewhat unique. The US Congress typically has the first and last word in any agreement between a government and the industries it regulates, with the notable exceptions being trade agreements and FDA's user fee agreements. FDA's user fee agreements are hashed out in direct negotiations between FDA and each of the respective industries it regulates. Congress is then given the draft of the user fee bill for final approval, which it must approve to become law, and must be signed by the President. Stakeholders involved in the negotiating process for past user fee agreements and who are supportive of it argue that this process results in an agreement that is tenable for both parties, and prevents the user fee agreements from becoming politicized or heavily modified by legislators lacking a deep understanding of the drug approvals process. Critics argue,

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78 In this context, see, for example, Rena M. Conti & Ernst R. Berndt, *Specialty Drug Prices and Utilization After Loss of U.S. Patent Exclusivity, 2001-2007* (National Bureau of Economic Research, Working Paper No. 20016), Mar. 2014, http://www.nber.org/papers/w20016 (accessed Aug. 10, 2017); and Christopher Stomberg, *Drug Shortages, Pricing, and Regulatory Activity* (National Bureau of Economic Research, Working Paper No. 22912), Dec. 2016, http://www.nber.org/papers/w22912 (accessed Apr. 21, 2017).

79 For further discussion, see Ernst R. Berndt et al., *The Landscape of U.S. Generic Prescription Drug Markets, 2004-2016* (National Bureau of Economic Research, Working Paper No. 23640), July 2017, http://www.nber.org/papers/w23640 (accessed Feb. 27, 2018).

80 We are indebted to Kurt R. Karst of Hyman, Phelps & McNamara PC for discussion on these issues, but are solely responsible for their accuracy.

however, that the public interest is not directly represented in the negotiations, and related industry officials, particularly from small businesses, worry their interests are not well represented in the largely bilateral bargaining process. Representatives of small CMOs have complained that their interests were not well represented in the GDUFA I negotiation process that instead included larger generic drug manufacturers.[81,82] Supporters of the current negotiation process point out, however, that the reauthorization process is also controlled in part by federal legislation, the *Federal Food, Drug and Cosmetic Act*, that requires FDA to request 'public input on the reauthorization' prior to starting any negotiations with industry. In addition, FDA is required to hold a public meeting during which time the public may comment on the reauthorization process and recommend changes to be made to the upcoming user fee agreement and accompanying Commitment Letter that describes in detail the commitments to be carried out by FDA. In particular, FDA asks two questions of the public: (i) What is your assessment of the overall performance of the GDUFA program to date? And (ii) What aspects of GDUFA should be retained, changed, or discontinued to further strengthen and improve the program?[83]

On April 21, 2015, with expiry of GDUFA I in October 2017 approaching, FDA announced it would be accepting comments from the public regarding the first reauthorization of GDUFA I to GDUFA II at a public meeting on June 15, 2015. At that and subsequent public meetings, FDA made public its track record in meeting GDUFA I approval, filing, correspondence, and communications commitment metrics.[84] For example, at her presentation at the Fall 2016 Technology meeting of the Generic Pharmaceutical Association ('GPhA')—later renamed the Association for Accessible Medicines, Director of the Office of Generic Drugs at the FDA, Kathleen Uhl, summarized FDA's position with a prominent slide, announcing '**To date, FDA has met or exceeded EVERY formal negotiated GDUFA goal**' (boldface and caps in original slide).[85] This was a remarkable achievement, she argued, for while FDA had projected receiving 750 ANDA applications annually for the 2013–2016 five year GDUFA I program, the

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81 See, for example, Pressman, *supra* note 75; Roth, *supra* note 75; and Glessner, *supra* note 44.

82 Until 2000, there were three generic trade associations: the Generic Pharmaceutical Industry Association (GPIA), the National Association of Pharmaceutical Manufacturers (NAPM), and the National Pharmaceutical Alliance (NPA). According to Kirking et al. [2001, pp. 581-2], 'GPIA and NAPM placed greater emphasis on scientific issues and NPA on sales and marketing issues. In addition, NAPM was more highly representative of the suppliers of raw materials'. In 2000, GPIA and NPA agreed to merge forming the Generic Pharmaceutical Association (GPhA). NAPM initially declined to participate 'because it felt its members would be underrepresented; two previous merger attempts had failed as well'. But then in 2001 NAPM joined GPhA. In 2017 GPhA changed its name to the Association for Accessible Medicines. For discussion, see Duane Kirking et al., *Economics and Structure of the Generic Pharmaceutical Industry*, 41 J. Am. Pharm. Assoc. 578–84 (2001).

83 Alexander Gaffney, *FDA Kicks off Generic Drug User Fee Reauthorization Process*, News, Regulatory Affairs Professionals Society, Apr. 21, 2015, page 3 of 6, https://www.raps.org/news-articles/news-articles/2015/4/fda-kicks-off-generic-drug-user-fee-reauthorization-process (accessed Feb. 28, 2018).

84 *Id.* pages 3 and 4 of 6. Annual GDUFA Performance Reports were also made public. For such annual reports for FY 2013 thru FY 2016, see US Food and Drug Administration, *GDUFA Performance Reports,* https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReportsUCM541866.pdf (for FY 2016), UCM493026 (for FY 2015), UCM451179 (for FY 2014), and UCM384177 (for FY 2013). https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm379854.htm (accessed Aug. 19, 2017).

85 Uhl, *supra* note 18, slide 11 of 84.

actual number exceeded 750 in four of the five years, hitting a maximum of 1473 submissions in FY 2014, and reaching a cumulative sum of 4936 submissions, 1186 or 32% more than projected and budgeted.[86] In terms of the GDUFA I backlog commitment to issue a 'first action' communication for 90% of the 2866 original ANDAs and 1877 PAS supplements in October 1, 2012 on or before by September 30, 2017, CDER Office of Generic Drugs Director Uhl announced that 'FDA hit the 90% 'GDUFA Backlog' Metric **15 months AHEAD of schedule**' (boldface and underline in original slide).[87] An earlier GDUFA Annual Report[88] provided a table showing FDA progress toward meeting the backlog goal.

In her penultimate slide summarizing FDA's perspective on meeting its GDUFA commitments, CDER Office of Generic Drugs Director Uhl stated: '**FDA Delivering on GDUFA**' and added bullets declaring 'FDA is fulfilling its GDUFA commitments; in many cases, going above and beyond our negotiated commitments; We are building a robust, modern generic drug regulatory program—Sustainable and predictable, Clear and consistent communications, Fairness across applications and applicants'.[89]

Although leadership lavished public praise on the agency's achievement of its GDUFA I performance goals, FDA also recognized areas for improvement. For example, volatility in the annual number of new one-time only ANDA receipts, and in the number of API and FDF facilities from its self-identification program, created annual budget uncertainties that affected the agency's ability to make long-term commitments both in its planning and hiring. As discussed earlier in the context of facility counts, the number of domestic FDF facilities fell 27% between 2013 and 2017—with the year-to-year changes varying in sign, while the domestic API facilities fell 21% over the same time period, increasing in two years but decreasing in two other years. ANDA application one-time user fees also varied substantially across years; while FDA budgeted for 750 ANDA receipts annually, the actual annual number varied by a factor of 2.7 from 539 in FY 2015 to 1473 in FY 2014.[90] For FDA, this revenue volatility raised the issue of whether there was an alternative GDUFA user fee structure that would yield a more predictable and stable annual flow of user fee revenues.

A number of criticisms of GDUFA I were also voiced from outside the agency. For example, news items indicated some contract manufacturers who provided API or FDF to generic manufacturers as well as chemicals to other clients, felt blindsided by the substantial FDF, and to a lesser extent, API annual GDUFA facility fees. President of the Pharma & Biopharma Outsourcing Association, Gil Roth, remarked, 'We have a single generic client that we do a short run of production for. Why are we charged the same as a Teva facility that pumps out a billion tablets?' Another commented, 'At least a flat tax is based on a percentage, either of revenue or profit. This is a flat fee, which makes it a regressive tax on smaller businesses, both contract manufacturers and small generics companies'.[91] A representative of a larger contract manufacturers with no internal generic ANDA holdings was quoted as saying, 'It'll be great if this results in ANDAs

86 *Id*. slide 12 of 84.
87 *Id*. slide 14 of 84.
88 U.S. Food and Drug Administration, *supra* note 61, page 14 of 26 plus appendices.
89 Uhl, *supra* note 18, slide 82 of 84
90 *Id*. slide 12 of 84.
91 As quoted in Roth, *supra* note 75, page 2 of 24.

getting approved more quickly, but the amount of business that contract manufacturers will gain from this isn't likely to pay off for years'. The result, he contended, is that costs for generics will increase, at least for smaller-run, specialty products. 'We'll see contract manufacturers exit generics, and those short runs will have to be handled by larger companies that aren't interested in them and will charge a heavier premium'. For those contract manufacturers that have an internal line of generic products in addition to their contract manufacturing work, perceptions of the burden of API and FDF facility fees were ones of resignation. Said one, 'We look at it this way: we'd have to pay the Facility Fee anyway for our own line. We're not happy about it, but if it improves approval times, then we could still benefit'.[92] Still another added, 'It might get worse as contract manufacturing organizations drop out of the program due to marginal profits. There are many winners with this program, but it will cut out the smaller players, especially the smaller international suppliers'. The President of the Pharma & Biopharma Outsourcing Association remarked, 'If I pay this fee, it's because I'm expecting to get revenues from pending products. I've budgeted generics that our clients filed nearly three years ago, but have yet to be approved. If this speeds up that process, and we can recognize that revenue soon, I'm fine with the fees'.[93]

One commentator, observing that the major stakeholders involved in the GDUFA user fee negotiations were the US's GPhA, the European Fine Chemicals Group, and the Society of Chemical Manufacturers and Affiliates' Bulk Pharmaceutical Task Force, questioned why it was that the GDUFA I negotiations resulted in Facility Fee invoices going directly to facility fee owners rather than to ANDA filers. Was that an instance of 'If you're not at the table, then you're on the menu?' He added, 'It's possible that the negotiating parties simply forgot about or were oblivious to the presence of "pure-play" CMOs that help manufacture generic drugs, especially those in short runs. It's also possible that GPhA's negotiators saw that millions of dollars of the annual GDUFA FDF contribution could be passed along to a subset of companies that had no voice at the bargaining table'. The commentator quoted a CMO industry lawyer as saying, 'I wouldn't be shocked if the big guys helped write the laws to squeeze the smaller generic companies and dump fees on pure-play manufacturers. I find it suspicious that GDUFA is modeled after PDUFA but doesn't include any waivers and charges sites directly. That's not an accident'.[94]

Already in October 2015, FDA began negotiations with industry and monthly discussions with patient and consumer groups concerning reauthorization to GDUFA II, with expiration of GDUFA I scheduled for September 30, 2017. Altogether, FDA had 28 meetings with industry between October 7, 2015 and August 24, 2016; 6 meetings with the fee modeling subgroup between June 28, 2016 and August 4, 2016; and 4 meetings with the FDA-Industry Small Business Subgroup. As required statutorily, FDA also held monthly discussions with representatives of patient and consumer advocacy groups during the GDUFA II reauthorization process. Minutes from all these meetings

92 *Id.* page 3 of 24.
93 *Id.* page 4 of 24.
94 *Id.*

are publicly available.[95] FDA also held two public meetings related to the reauthorization of GDUFA II. Each meeting was announced in the *Federal Register* along with the opening of a docket to allow public comments. The first meeting was held on June 15, 2015, prior to negotiations with industry, to allow the public to present its views on the reauthorization, including specific suggestions for changes. The second meeting was held on October 21, 2016, after negotiations with industry, to allow the public an opportunity to see and comment on the recommendations developed by FDA and the industry prior to the recommendations being sent forward to Congress. Meeting materials and comments submitted for these public meetings are available online,[96] as is FDA's summary of views and comments received at the October 21, 2016 public meeting and the 15 written comments submitted to the public docket.[97] The public document subsequently closed on November 16, 2016.

At the initial GDUFA II reauthorization public meeting, both FDA and industry acknowledged problems and successes, with varying and not necessarily consistent opinions. For example, in contrast to the laudatory statements from Office of Generic Drug Director Kathleen Uhl, David Gaugh, a senior vice president at the GPhA, declared 'We are hitting the marks that we wanted to, but execution is still lacking'.[98] One prominent issue the two sides depicted differently involved the backlog of the nearly 3000 ANDAs filed prior to implementation of GDUFA I on October 1, 2012 (Fig. 1). According to Gaugh, the backlog as of June 2015 was more than 4000 applications, and its growth has been accompanied by a sharp rise in median review times to 48 months in 2015 from 31 months in 2012. Gaugh was quoted as saying, 'It is industry opinion that the FDA is falling short of meeting its commitment to GDUFA goals'. Distinguishing between pre-GDUFA ANDA and PAS filings (those before October 1, 2012) and those filed after that date, FDA documented it had made very substantial progress in reducing the backlog of pre-GDUFA filings, noting that it had committed to eliminating 90% of them by September 30, 2017, and according to the Director of the Office of Generic Drug Policy, Keith Flanagan, 'We are way ahead of schedule on that commitment'.[99] Regarding ANDA submissions filed after October 1, 2012, FDA suggested the backlog on those filings was attributable in large part to a much greater than expected number of ANDA applications, with the number of 2012 and 2013 being about 1000, followed by almost 1500 in 2014, much larger than the 750 per year that was expected at the time of the initial GDUFA legislation. Regardless of those expectations, GPhA took

[95] See U.S. Food and Drug Administration, *GDUFA Reauthorization Negotiation Sessions*, https://wayback.archive-it.org/7993/20171103063004/https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm256662.htm (accessed Feb. 28, 2018). For minutes of GDUFA Reauthorization Stakeholder meetings with representatives of patient and consumer advocacy groups, see U.S. Food and Drug Administration, *GDUFA Reauthorization Stakeholder Meetings*, https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm466008.htm (accessed Apr. 24, 2017).

[96] See U.S. Food and Drug Administration, *GDUFA Reauthorization Public Meetings*, https://wayback.archive-it.org/7993/20171103072201/https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm444958.htm (accessed Feb. 28, 2018).

[97] U.S. Food and Drug Administration, *GDUFA II Public Comments*, http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm535884 (accessed Apr. 24, 2017).

[98] As quoted by Jeff Overley, *Generic-Drug Makers Urge Changes to User-Fee Law*, LAW360.COM, June 15, 2015, page 2 of 5, http://www.law360.com/articles/668203/generic-drug-makers-urge-changes-to-user-fee-law (accessed Sept. 12, 2015).

[99] *Id.*

Cumulative Percent of Backlog Issued First Action

Submission Type	Backlog as of October 1, 2012	FY 2013	FY 2014	FY 2015	FY 2016
ANDA	2866	31%	60%	80%	94%
PAS	1877	40%	73%	86%	93%
Total	4743	34%	65%	82%	93%

Figure 1. Cumulative percent of FDA ANDA and pas backlog issued first action. Notes: ANDA is Abbreviated New Drug Application, PAS is Prior Approval Supplement. **Source:** Reprinted from US Food and Drug Administration, 'FY 2016 Performance Report to Congress for the Generic Drug User Fee Amendments' page 14 of 26 plus appendices, https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm541886.pdf (accessed April 26, 2017).

issue with work on implementation, saying that FDA has $277 million in unused funds as of 2015 (GDUFA I generated approximately $300 million annually). According to Gaugh, 'Given the sluggish pace of reviews and the steadily growing backlog, it is especially confounding that the FDA still has $277 million in unused funds from the generic industry that could be applied to site inspections or approvals'.[100]

The ambiguity of the agency's performance during GDUFA I can be appreciated by reviewing FDA's track record of annual final and tentative ANDA approvals. Fig. 2 reproduces a slide from CDER Office of Generic Drugs Director Uhl's October 24, 2016 presentation at the Generic Pharmaceutical Association Fall Tech Meeting.[101] Between FY 2010 and 2012, FDA on average gave final or tentative approval to 594 ANDAs per year. In the years after GDUFA I implementation (FY 2012–2015), the average annual number of final or tentative approvals fell 7.6% to 549 per year, only to increase substantially to 835 in FY 2016. Recall that in the first three years of GDUFA I (FY 2013–FY 2015), the number of new ANDA applications received by FDA averaged about 1000, considerably more than the 750 it had projected and budgeted for these years. So even as it worked diligently to eliminate the substantial backlog of pending ANDAs (ANDAs that likely were quite complex and required considerable attention by reviewers), FDA was receiving unexpectedly large numbers of new ANDA applications. Although FDA ultimately succeeded in eliminating 90% of the backlog before September 30, 2017, as it had committed for GDUFA I, with its attention diverted to meeting the backlog commitment, the number of new pending ANDAs grew very rapidly, increasing their time to final or tentative approval. Thus, both FDA's laudatory pronouncements and industry's complaints about the accumulating number of newly submitted ANDAs can be appreciated and reconciled with each other.

Other GDUFA I elements receiving criticisms included levying annual facility fees for CMOs producing only one generic drug in a given year. According to President of the Pharma & Biopharma Outsourcing Association, that low threshold for triggering

[100] *Id.* pages 2 and 3 of 5. Note that since the number of new ANDAs filed in 2014 was 1473 rather than the expected 750, thereby increasing FDA user fee revenues, it is not surprising that in 2015 the FDA had a substantial amount of unused funds on hand.

[101] Uhl, *supra* note 18, slide 18 of 82.

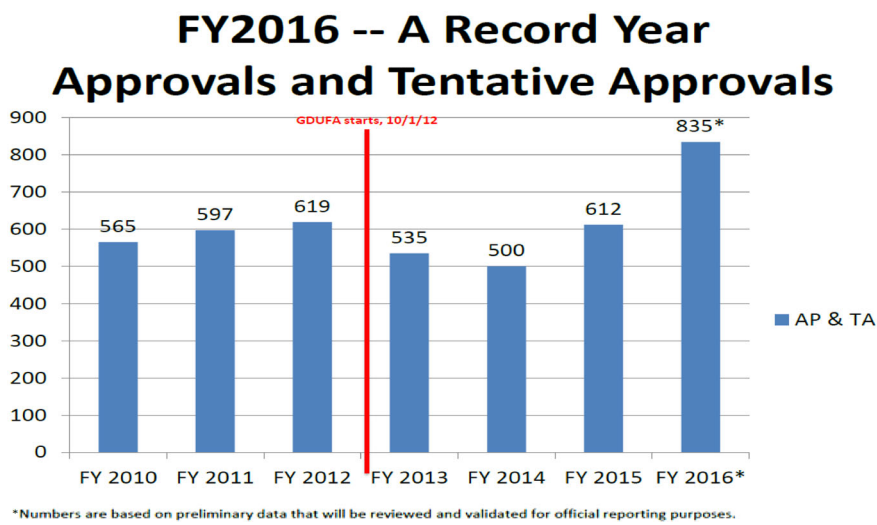

Figure 2. FY2016 – ANDA approvals and tentative approvals. Notes: ANDA is Abbreviated New Drug Application, AP is approvals, TA is tentative approvals. Source: Reprinted from K. Uhl, M.D., Director, Office of Generic Drugs (OGD) Director's Update, 'Meeting GDUFA Commitments—Going for GOLD', Powerpoint presentation, GPhA Fall Tech Meeting, October 24, 2016, slide 18 of 82, at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM527918 (accessed Apr. 23, 2017).

fees is a disincentive to accept work from the generics industry and could end up exacerbating shortages of sterile injectables and other important products. 'Our take is that a flat fee isn't fair' Roth said, 'In the next version of GDUFA, we'd like to see some sort of adjustment'. Noting that manufacturers of FDFs pay heftier fees under GDUFA I than companies that merely produce API, industry representatives argued that an active ingredient is treated as a FDF for fee purposes if it is combined with even one other drug component (eg, a combination of two active ingredients but not yet in a tablet or capsule formulation), and that this fee structure results in unsustainable fees. According to Alan Nicholls of the Bulk Pharmaceutical Task Force, a project of the Society of Chemical Manufacturers and Affiliates, 'The margins for manufacturers for these products are just not commensurate with this level of fee'.[102]

Other speakers suggested GDUFA II waive or relax fees for small businesses, arguing that many cannot afford the law's fees. Transparency issues were also raised at the hearing, as FDA had agreed under GDUFA I to improve its communications with applicants in various ways that some hearing commentators suggested had not fully materialized. According to GPhA's Gaugh, 'Communication and feedback are not occurring, placing industry in the dark'. Attention at the hearing also focused on FDA's increased activity in inspecting foreign manufacturing sites, quite frequently resulting in Form 483 citations and occasional plant closings or suspension of licenses to import into the US. Although the agency was lauded for increased overseas enforcement, there was some discussion of whether regulators have slipped domestically, with Nicholls from the Bulk

[102] *Id.* page 3 of 5.

Pharmaceutical Task Force warning that failure by US manufacturers to be inspected every three years can result in their imports being blocked in other countries.[103]

Based on these and other public meetings, FDA and industry representatives completed negotiations and reached tentative agreements for GDUFA II.[104] GDUFA II was authorized by the US Congress on August 3, 2017 and took effect on October 1, 2017.

V. MAJOR USER FEE PROGRAM CHANGES FROM GDUFA I TO GDUFA II

There are five important changes in the user fee design between GDUFA I and GDUFA II: (i) no PAS fee; (ii) annual facility fee due only once an ANDA is approved, and not while ANDA application is pending; (iii) if a site is both an API and an FDF manufacturing facility, it only pays the FDF fee; (iv) a new CMO fee for those companies making FDF but not holding an ANDA; and (v) a new ANDA annual holder program fee.[105]

Much of the GDUFA II revisions involved attention to small business concerns.[106] A basic first challenge was defining a small business—was it based on number of employees, sales revenues, or number of ANDAs? While the generic drug industry includes a substantial number of small firms, most applications and facilities are part of large firms. Setting parameters for small business user fee relief was challenging because apparently there were a large number of small businesses in the industry (although there was considerable uncertainty about the size distribution of companies), and both industry and FDA recognized that verifying the criteria could pose a burden on the agency and industry, particularly for small privately held companies. These considerations led FDA and industry negotiators to conclude that traditional models of small business relief were not the best or most efficient way to address needed relief. This recognition fed into a broader fee discussion yielding three recommendations: a tiered annual program fee, no payment of annual facility fees while an ANDA application was pending at FDA, and an annual facility fee discount to FDF contract manufacturing organizations.[107] Specifically, under GDUFA I a facility incurred an annual facility fee if it was referenced in a pending or approved ANDA. This meant a facility referenced only in a pending ANDA submission would incur an annual facility fee even though it had no generic drug revenue stream. Under GDUFA II, a facility will be levied an annual user fee only once it is identified in an approved ANDA submission.

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[103] *Id.*

[104] The legislation providing for reauthorization required a final public meeting to present the tentative agreement for public comments, followed by an open time period for public views and comments, responses by industry and FDA, and notification of the closing of the docket before sending the agreement to Congress for legislative approval, and then for Presidential signature. The final public meeting was held on Oct. 21, 2016. The transcript of the public meeting and the written comments submitted to the docket are on FDA's website as is a summary of the public comments. A webinar focusing on PDUFA II was held Oct. 28, 2016. Slide presentations by FDA officials from both meetings are publicly available.

[105] U.S. Food and Drug Administration, *GDUFA II Overview*, CDER SBIA Webinar Series, Oct. 28, 2016, slide 16 of 17, http://sbiaevents.com/files/GDUFA-II-WebinsrWebinarWebinar-Oct-2016.pdf (accessed Apr. 26, 2017).

[106] U.S. Food and Drug Administration, *GDUFA II Public Meeting*, Oct. 21, 2016, slide 20 of 80, http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm526282 (accessed Apr. 26, 2017). Text in square brackets not in original slide.

[107] *Id.* slides 21 and 22 of 80.

Furthermore, ANDAs are the primary workload driver of the GDUFA program. While GDUFA I assumed FDA would receive approximately 750 ANDAs per year, in the first four years of GDUFA I the number of ANDAs received was about 1000 per year. To address the increased workload, FDA hired additional staff and projected it would spend about $430 million in user fee funds in the final FY 2017 of GDUFA I (originally it had projected about $300 million annually for the five-year GDUFA I program, but adjusted annually for inflation). During negotiations, FDA and the industry agreed that user fees in GDUFA II should total almost half a billion dollars annually ($493.6 million), adjusted each year for inflation.[108] While application volume can fluctuate considerably from year to year, there is a relatively stable universe of ANDA sponsors. Therefore, to maintain a predictable fee base and better align fee responsibility with program costs and fee-paying ability, FDA and industry decided to shift the user fee burden more toward annual ANDA program fees, and away from one-time ANDA submission fees. All ANDA sponsors with one or more approved ANDAs would pay an annual fee. However, the amount of the annual ANDA program fee would vary depending on the number of ANDAs owned by an ANDA sponsor and its affiliates: large (20 or more) approved ANDAs are assessed 100% of the ANDA annual fee; medium (sponsor and its affiliates holding between six and 19 approved ANDAs) would be assessed 40% of the full annual fee; and small (sponsor and its affiliates holding five or fewer approved ANDAs) would be assessed 10% of the full annual fee.[109]

Implementation of such a tiered annual ANDA program fee depending on the number of ANDAs owned by a sponsor and its affiliates required defining what is an affiliate. GDUFA negotiators proposed that 'The term "affiliate" means a business entity that has a relationship with a second business entity if, directly or indirectly—(A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has power to control, both of the business entities'.[110]

One other small business consideration involved CMOs. Under GDUFA II, within the FDF facility category, CMOs would pay only one third of the annual FDF facility fees paid by firms that manufacture FDF ANDA products at facilities which they themselves or their affiliates own. Foreign CMOs would continue to also pay the $15,000 foreign facility fee. Note that under GDUFA II, the CMO classification is carved out for the FDF manufacturers only. In particular, a CMO manufacturing API incurs a full annual API facility fee when referenced in approved submissions, but does not pay the annual fee.[111]

Finally, regarding PASs, in GDUFA I ANDA sponsors were required to pay a one-time PAS fee (about $35,000 in 2017), even if the PAS was requested by the FDA.

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[108] The $493.6 total million target revenue was comprised of ANDA annual program fees (35% of total, $172,760,000), one time ANDA filing fees (33% of total, $162,888,000), one-time DMF fees (5% of total, $24,680,000), annual API facility fees (7% of total, $34,552,000), and annual FDF facility fees (20% of total, $98,720,000). U.S. Food and Drug Administration, *supra* note 107, slide 10 of 17.

[109] *Id*. slides 60-61 and 65 of 80.

[110] U.S. Food and Drug Administration, *supra* note 107, slide 7 of 17.

[111] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Small Business and Industry Assistance, Division of Drug Information, Office of Communications, 'FDA Addresses Small Business Concerns in GDUFA II', R. Lal interview of G. Perez, CDER SBIA Chronicles, Jan. 26, 2017, pages 1 and 3 of 3, https://www.fda.gov/downloads/Drugs/.../SmallBusinessAssistance/UCM538414.pdf (accessed Apr. 26, 2017).

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

Figure 3. GDUFA I v. GDUFA II fee structure. Source: Reprinted from U.S. Food and Drug Administration, 'GDUFA II Public Meeting, October 21, 2016', slide 62 of 80, http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm526282 (accessed Apr. 26, 2017).

FDA's experience during GDUFA I indicated that the number of PAS submissions received was volatile and unpredictable. Moreover, the design and intent of the new ANDA annual program fee was viewed both by industry and FDA as an investment in the program—a program that would be recommending and evaluating PAS submissions on a regular basis through the life cycle of an ANDA. As a result, industry and FDA agreed to eliminate entirely the PAS fee in GDUFA II.[112]

Differences in the structure of user fees in GDUFA I and those enacted in GDUFA II are summarized in Fig. 3.[113] The most notable differences are that while annual FDF facility fees accounted for about 56% of GDUFA I collections and annual API facility fees 14%, making the two facility fees responsible for 70% of GDUFA I collectibles, in GDUFA II these annual facility fee categories will only contribute 20%, 7%, and 27% of collections, respectively. Offsetting these major GDUFA II reductions in annual FDF and API facility fees is the introduction in GDUFA II of annual ANDA holder program fees, which are projected to provide 35% of total GDUFA II collections. One other notable difference is the increased importance of one-time annual ANDA application fees, which in GDUFA I provided 24% of total user fee collections, but in GDUFA II increases to 33% of total user fee collections. Finally, while in GDUFA I there are no scale-related program fees, in GDUFA II total annual ANDA holder fees are tiered for small, medium, and large sponsors, holding 1–5, 6–19, or ≥20 ANDAs, respectively.

[112] U.S. Food and Drug Administration, *supra* note 108, slide 62 of 80.

[113] *Id.* slide 65 of 80.

VI. GDUFA NEW DATA COLLECTION EFFORTS AND INDUSTRY INSIGHTS

In order to estimate per-API facility and per-FDF facility user fees, to target inspections at foreign and domestic facilities in a fair and transparent manner, and more generally to be able to monitor whether facilities were compliant with cGMP, it was necessary for FDA to have access to comprehensive data covering the generic drug supply chain. According to one GDUFA authorization process observer, 'FDA admitted that it needed a better understanding of the world of generic drug makers and service providers'. Before GDUFA I, the self-identification initiative authorized by the GDUFA legislation sought partly to remedy this data shortfall, but even that depended on how many companies cooperated with the self-identification initiative. Noted one observer, 'In December 2012, at the end of the reporting period for self-identifying, the number of facilities on the list was below estimates of the universe of generic drug facilities. Based on facilities listed in ANDAs *between October 1 and December 2, 2012,* it appeared that *one in eight facilities failed to self-identify*. A two-week grace period helped improve the numbers, but they still fell short of the agency's initial estimates'.[114]

When asked how accurate were FDA's estimates of facility numbers based on the self-identification process and other data sources, a representative of FDA's Center for Drug Evaluation and Research was quoted as saying,

> Actually the facility estimates that were used in the negotiation were not terribly far off – but as we told industry clearly during the negotiation prior to GDUFA, FDA lacked a single comprehensive accurate database of all facilities involved in the manufacture of generic drugs, so we utilized the best information we had at the time. To the extent there were overestimations in any category, those would have been due to insufficiencies in the information that was available, and the fact that for years, firms have been very lax about removing facilities from FDA's registration database when they are no longer manufacturing drugs. It should also be noted that industry trade groups were unable to provide any more accurate estimates of the number of facilities that the ones that both sides used in the negotiation.[115]

The reporter went on to write, 'It's a chronic problem for the industry. Some of the people we spoke to for this article contended there are companies on the FDA's facilities list that they are certain no longer exist'.[116] Another observer noted that based on data provided by the self-identification process in GDUFA I, FDA was unable to determine whether the respondent was a CMO, a generic ANDA holder, or a hybrid manufacturer.[117]

These observations on the lack of an underlying comprehensive and up-to-date database held by FDA of generic manufacturers, ANDA holders, and other companies in the generic drug supply chain were reiterated by CDER Office of Generic Drugs Director Uhl who in commenting on the performance of the GDUFA I program, reported that as of September 2016, FDA estimated that currently there were approximately

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114 Roth, *supra* note 75, page 5 of 24. Italics in original.
115 *Id.*
116 *Id.*
117 Pressman, *supra* note 75, page 2 of 3.

10,000 approved ANDAs (but noted 'many approved ANDAs are not marketed')[118] and about 4000 unapproved ANDAs.[119] Based on a download of data from the FDA's Orange Book on January 7, 2016, Uhl provided a 'big picture' of that source's classification of 1328 drug ingredient products. According to Uhl, 867 (65%) of drug ingredients listed in the Orange Book were innovator drugs with approved competitors (NDAs and ANDAs), 313 (24%) were innovator drugs with no approved generics (NDAs), protected by patents or other exclusivity, 125 (10%) were innovator drugs (NDAs) with no approved generics and no ANDAs submitted, and 23 (<2%) were innovator drugs with pending ANDAs.[120]

Under GDUFA II, as under GDUFA I, data from annual self-identification responses are required to be submitted to the FDA from each facility each year between May 1 and June 1. These data are used to establish annual per FDF facility, annual per API facility, and annual per CMO facility charges, which are announced in July or August and are typically due on October 1. An entirely new set of ANDA ownership determination data will be necessary in order for FDA to implement the proposed GDUFA II tiered annual ANDA program fees, for the invoiced amount will depend on how many ANDAs are owned by each ANDA holder. Although FDA has information on who was the applicant who currently is holder of each approved ANDA, there is a consensus that many approved ANDAs are no longer marketed, and that given consolidation among ANDA holders over the years, the current ANDA owners may not be the same as those recorded on the initial approval or on subsequent communications between the industry and FDA. Consequently, in order to be able to implement GDUFA II in Fall 2017, FDA needed first to determine ownership of ANDAs.

In December 2016, FDA published a spreadsheet list of approved ANDAs on record at the agency as of November 14, 2016.[121] A *Federal Register* Notice asked ANDA holders to claim all ANDAs owned by them or their affiliates, to correct any errors on the spreadsheet and return corrections to FDA by February 2017. FDA announced it would publish in March 2017 the list of claimed ANDAs and their sponsors, the number of ANDAs claimed by each sponsor along with the tier to which those sponsors would tentatively be assigned for purposes of invoicing annual program fees, as well as a list of unclaimed ANDAs. Sponsors of both claimed and unclaimed ANDAs were requested to submit corrections to the list in April 2017; FDA committed to publish a corrected list in June 2017, and based on that corrected list, FDA committed to publishing and invoicing FY 2018 fees in August 2017, with annual fees being due on October 1, 2017.

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[118] A 2006 study by the U.S. Department of Health and Human Services, Office of Inspector General, found that about 28% of the products listed in the FDA's Listed Drug File Directory in 2005 were not listed at all as being actively marketed on the industry's First DataBank's National Drug Data File Plus that year. See U.S. Department of Health and Human Services, Office of Inspector General, The Food and Drug Administration's National Drug Code Directory, OEI—6-05-00060, Aug. 2006, p. 1.

[119] Uhl, *supra* note 18, slide 55 of 84.

[120] *Id*. slide 61 of 84. A note to the slide explains 'The unit of observation is the drug ingredient. Different useable forms (e.g., salts or esters) of the same core molecule are counted as separate drug ingredients; this does not differentiate between multiple dosage forms (e.g., capsules vs. tablets) for the same drug ingredient. Each drug ingredient is identified as having either multiple approved sponsors (the dark blue group) or a single approved sponsor'. Note also that since the Orange Book does not include BLAs, biologic molecules are not included in these counts.

[121] U.S. Food and Drug Administration, *Program Fee List – Excel file*, https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM531828.xlsx (accessed Apr. 5, 2017).

Table 4. Size Distribution of ANDA Portfolio Sponsors as of November 14, 2016.

ANDA Portfolio Size	*Number of Sponsors*	*Share of Sponsors (%)*	*Cumulative Number of Sponsors*	*Cumulative Share of Sponsors (%)*
1	237	35.1	237	35.1
2	112	16.6	349	51.6
3	53	7.8	402	59.5
4	34	5.0	436	64.5
5	28	4.1	464	68.6
6–10	61	9.0	525	77.7
11–50	108	16	633	93.6
51–150	33	4.9	666	98.5
>150	10	1.5	676	100

Notes: ANDA is Abbreviated New Drug Application.
Source: Authors' calculations from file that was originally available from the FDA website https://www.fda.gov/forindustry/userfees/genericdruguserfees/default.htm.

In late March 2017, FDA publicly released its list of ANDA sponsors, and the number of ANDAs held by each sponsor as of November 14, 2016.[122] The list named 676 sponsors who together held 9861 ANDAs, implying that a sponsor on average held 14.59 ANDAs. As seen in Table 4, the size distribution of number of ANDAs held was very left skewed with a disproportionate share of ANDA sponsors holding only a small number of ANDAs. In particular, 237 of the 676 ANDA sponsors (35.1%) held only one ANDA. More than two-thirds of the sponsors (68.6%) held five or fewer ANDAs, and 98.5% held 150 or fewer ANDAs. Ten sponsors (1.5%) held more than 150 ANDAs. The median number of ANDAs held was 2, and the modal number of ANDAs held was 1.

Unlike the sponsor distribution that was left-skewed in Table 4, as seen in Table 5 the ownership distribution was right skewed, with a small number of very large ANDA portfolio holders owning a disproportionate share of approved ANDAs. Of the total number of 9861 approved ANDAs, the share held by the ten largest (1.5% of 676) portfolio sponsors was a staggering 31.4%. These 10 largest sponsor portfolios were Fresenius Kabi USA Inc (178 ANDAs), Teva Pharmaceuticals USA (194), Sun Pharmaceutical Industries Inc (213), Teva Pharmaceuticals USA Inc (219), Aurobindo Pharma

[122] In correspondence with Donald Dobbs, a Drug Information Specialist at the Division of Drug Information, Center for Drug Evaluation and Research at the FDA on Apr. 12, 2017, the authors were informed the file was originally available from the FDA website https://www.fda.gov/forindustry/userfees/genericdruguserfees/default.htm, but that file has apparently been deleted and replaced with an updated file as of April 30, 2017 (see UCM531828 reference below). A hard copy of the apparently deleted file and email correspondence with Mr. Dobbs is available from the lead author upon request.

Table 5. ANDA Portfolio Size and Ownership Distribution as of November 14, 2016.

ANDA Portfolio Size	*Number of Sponsors*	*Share of Sponsors (%)*	*Number of ANDAs Held*	*Share of ANDAs Held (%)*
1–5	464	68.8	896	9.1
6–10	61	9.0	461	4.7
11–50	108	16.0	2603	26.4
51–150	33	4.9	2808	28.5
>150	108	1.5	3093	31.4
TOTALS	676	100	9861	100

Notes: ANDA is Abbreviated New Drug Application.
Source: Authors' calculations from file that was originally available from the FDA website https://www.fda.gov/forindustry/userfees/genericdruguserfees/default.htm.

Ltd (225), Hospira Inc (238), Apotex Inc (253), Mylan Pharmaceuticals Inc (495), Sandoz Inc (506), and Watson Laboratories Inc (572).

The variability in ANDA portfolio sizes and ANDA ownership shares based on FDA Orange Book data as of November 14, 2016, can therefore be summarized as follows: while 237 of 676 sponsors (35.1%) held only one approved ANDA, together these most prevalent small portfolio size sponsors only accounted for 2.4% of all approved ANDAs. In contrast, the 10 largest portfolio sponsors (1.5% of 676) together accounted for 3093 of the 9861 (31.4%) of all approved ANDAs.

Notably, the above list of the 10 largest ANDA portfolio holders suggests that some of these top 10 may be affiliated with each other (eg, Teva Pharmaceuticals USA, and Teva Pharmaceuticals USA Inc),[123] so that the true portfolio ownership size distribution was likely even more concentrated than that implied in the Orange Book as of November 14, 2016. Slight corporate name changes, product exits from consolidations through mergers and acquisitions and intrafirm divisions, entire company exits, and other corporate governance changes over time could alter the ANDA sponsor ownership distribution considerably.

Presumably aware of this possibility, in December 2016 FDA asked its universe of ANDA holders to examine this list and make corrections to take into account affiliated organizational and other inaccuracies, and respond to the agency by February 2017 with a corrected list of claimed ANDAs. This was done, and consistent with its commitment, in late March 2017 FDA provided a revised list of ANDA holders as of March 10, 2017. This list was updated yet again and published on May 22, 2017, providing a revised list of ANDA holders as of April 30, 2017.[124] The latter list distinguished those ANDAs claimed and those ANDAs not claimed by sponsors, as well as adding to the list of sponsors and ANDAs the cumulative number of those ANDAs approved between November 14, 2016 and April 30, 2017. Whereas the November 14, 2016 file identified

[123] Another apparent TEVA-related sponsor listed on the Nov. 14, 2016 spreadsheet was Teva Parenteral Medicines Inc.

[124] U.S. Food and Drug Administration, *supra* note 123.

Table 6. Size Distribution of Claimed ANDA Portfolio Sponsors and Ownership Distribution as of April 30, 2017.

ANDA Portfolio Size	*Number of Sponsors*	*Cumulative Share of Sponsors (%)*	*Number of ANDAs*	*Share of ANDAs Held (%)*	*Cumulative Number of ANDAs*
1	18	18	17	0.2	17
2	7	25	16	0.2	33
3	6	31	18	0.2	51
4	7	38	28	0.4	79
5	3	41	10	0.1	89
6–10	10	51	82	1.0	171
11–19	8	59	119	1.5	290
20–50	16	75	444	5.6	734
51–150	11	86	1051	13.2	1785
151–300	7	93	1478	18.6	3263
>300	7	100	4703	59.0	7966

Notes: ANDA is Abbreviated New Drug Application.
Source: Authors' calculations from 'Program Fee List—Excel file'. Available at https://www.fda.gov/forindustry/userfees/genericdruguserfees/UCM531828.xlsx (accessed July 22, 2017).

676 distinct ANDA applicant sponsors, after the April 30, 2017 responses were tallied, the number of distinct ANDA applicants and parent company sponsors was reduced by 30% to 478 (100 claimed ANDA parent companies, and 378 unclaimed). The claimed size distribution of sponsors and ANDAs is presented in Table 6.

Although industry's response rate to FDA's data request regarding claimed ANDAs was rather modest—by April 30, 2017 an 18.8% response rate (100 of 676), these 100 parent company sponsors claimed ownership of 7966 ANDAs. The average number of claimed ANDAs held by each parent company sponsor was 79.66, the median was 10, and the mode was only one ANDA. As seen in Table 6, those parent company responders claiming ownership of ANDAs were a select group of sponsors, predominantly consisting of those with large ANDA portfolios. While 67.3% of ANDA sponsors listed in the Orange Book as of November 14, 2016 had a portfolio of five or fewer ANDAs (Table 4), among those parent company sponsors responding by April 30, 2017 only 41% had a portfolio of five or fewer ANDAs (Table 6). By contrast, while only 1.5% of Orange Book sponsors as of November 14, 2016 held portfolios of greater than 150 ANDAs (Table 4), a much larger 14% (14 of 100) responding parent company sponsors claimed ownership of portfolios consisting of more than 150 ANDAs (Table 6). An implication is that those not responding to the FDA data request were predominantly small ANDA portfolio companies, perhaps acquired by others or no longer in existence.

The disproportionate share of ANDAs claimed by parent company sponsors with large portfolios is also displayed in Table 6. While 14% of sponsors claimed ownership of portfolios consisting of greater than 150 ANDAs (7% between 150 and 300, and 7% greater than 300), together they accounted for 6181 (1478 plus 4703) of the 7966 of the total claimed ANDAs (77.6%) as of April 30, 2017. The 10 largest claimed ANDA holders as of April 30, 2017 included Teva Pharmaceuticals USA Inc (1611 ANDAs), Mylan Inc (668), Novartis Corporation (649), Sun Pharmaceuticals Inc (585), Hikma Pharmaceuticals PLC (495), Endo International PLC (376), Aurobindo Pharma Ltd (319), Apotex Inc (282), Pfizer Inc (266), and Perrigo Company PLC (224). Together these 10 sponsors claimed 5475, or 69% of the 7966 total claimed ANDAs as of April 30, 2017. Hence, while 41% of claimed ANDA holders had portfolios of five or fewer ANDAs together comprising just over 1% of all claimed ANDAs, the largest 10% of claimed ANDA portfolio holders together accounted for 69% of all claimed ANDAs.

Although implicit, it is also of interest to examine more closely the size distribution of ANDA portfolios, and the ownership distribution for those ANDAs still unclaimed by applicants or their parent companies. In total, as of April 30, 2017, 378 sponsors identified in the Orange Book failed to claim ownership of 1961 ANDAs. The mean number of unclaimed ANDAs held was 5.19 per sponsor, the median was 2, and the mode was 1 (data not shown). Employing the GDUFA II ANDA program fee structure, we observe that 78.9% of the nonclaimants had 'small' portfolios (1–5 ANDAs), 14.7% had 'medium' portfolios (6–19 ANDAs), and 2.4% had 'large' portfolios (20 or more ANDAs). The share of the total number of unclaimed ANDAs held by these companies was 27.5%, 26.7%, and 46.8%, respectively. The five largest portfolio applicants not claiming ANDA ownership were Glenmark Pharmaceuticals Ltd (86 ANDAs), Wockhardt Ltd (78), Luitpold Pharmaceuticals Inc (71), Upsher-Smith Laboratories Inc (53), and Sagent Pharmaceuticals Inc (50). Hence, the vast majority (almost 80%) of nonclaiming ANDA holders were companies with small ANDA portfolios, together accounting for only about a quarter of all unclaimed ANDAs.

In late March 2017, FDA sent back to Orange Book-identified ANDA sponsors its lists of claimed and unclaimed ANDAs. A final list of claimed and unclaimed ANDA holders as of September 8, 2017 was publicly released in September 2017 to facilitate invoicing for GDUFA II user fees due October 1, 2017.

For FY 2018, the estimated number of CMO and FDF facilities was 253 domestic and 385 foreign, while the estimated number of API facilities was 79 domestic and 513 foreign, yielding a total number of facilities at 1150, with 332 being domestic and 818 foreign. These estimates represent a considerable contraction in the total number of facilities relative to FY 2018 (see Table 2—about a 7% decline in the number of domestic and a more substantial 26% decline in the number of foreign facilities, with approximately equal proportionate declines in foreign FDF and API facilities). For FY 2018, the FDA estimated the number of initial letters of reference to a DMF it would receive would increase considerably from 369 in FY 2017 to 516, while the estimate of the number ANDAs it will receive is 938, with the number of full application equivalents being 948. Given the estimated number of facilities and overall FDA budgets, the FY 2018 (FY 2017) one-time application fees for an ANDA are $171,823 ($70,480), PAS $0 ($35,240), and DMF $47,829 ($51,140); annual API facility fees for FY 2018 (FY 2017) are $45,367 ($44,234) domestic and $60,367 ($59,234) foreign, while for FDF

facilities they are $211,087 ($258,646) domestic and $226,087 ($273,646). New in FY 2018 are the annual CMO facility fees ($70,362 domestic and $85,362 foreign), as well as the annual GDUFA program fees ($1590,792 for large ANDA holders, $636,317 for medium ANDA holders, and $159,079 for small ANDA holders).[125]

As we noted above, both FDA and industry personnel believe a substantial number of approved ANDAs are no longer marketed, but it is unknown how large is their number. There could be many reasons for no longer marketing an approved ANDA. Companies with approved ANDAs may have decided not to market their approved ANDAs after observing a smaller potential market than when originally applying for ANDA approval. Companies may no longer exist, either because they were acquired or because they simply closed down. Other companies may continue to exist, but may have decided some time ago to terminate the manufacturing and marketing of their ANDAs.[126] More insight on reasons for not claiming ANDAs may be gained when FDA releases its final list of claimed and unclaimed in 2017 or 2018.

VII. FINAL THOUGHTS AND OBSERVATIONS

In large part because of congressional passage of the GDUFA legislation, FDA has been mandated to collect and publish data concerning various aspects of the US generic prescription drug industry. Even though it maintains the Orange Book registry and Directory of all approved prescription drugs, FDA has had only a very limited knowledge of who are the ANDA holders, how many of them still market the drug, who manufactures the API and FDF formulations—Is it the ANDA sponsor or a CMO?—and where the various manufacturing processes actually occur.[127] Notably, the FDA Office of Generic Drugs has devoted a considerable portion of its GDUFA I user fee revenues to compiling, curating, and publishing these types of data. Not only does the availability of such data facilitate reliable and timely FDA regulatory oversight and monitoring, but making the data publicly available enables industry participants and analysts, as well as other researchers, to carry out independent analyses of the structure, conduct, and performance of the various industry and regulatory participants.

Based on new data available due to GDUFA efforts, we have learned that the manufacturing of API is almost entirely off-shore, that the majority of FDF manufacturing facilities are also foreign, what generic pharmaceutical manufacturing occurs domestically is primarily FDF rather than API manufacturing, and that trends in these activities

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[125] U.S. Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2016-N-0007], Generic Drug User Fee Rates for Fiscal Year 2018, Aug. 29, 2017, https://federalregister.gov/d/2017-18377 (accessed Feb. 27, 2018).

[126] Moreover, some companies may temporarily discontinue manufacturing and marketing a product, waiting to re-enter if business prospects for that product improve. This contestable market phenomenon – the threat to re-enter – may contribute to disciplining the pricing behavior of the incumbent producers. We discuss this contestable market phenomenon in greater detail in Ernst R. Berndt et al., *The Landscape of U.S. Generic Prescription Drug Markets, 2004-2016* (National Bureau of Economic Research, Working Paper no. 23642), Aug. 2017.

[127] For further discussion, see Rena M. Conti & Ernst R. Berndt, *Who Makes This Drug? The Public Costs of Keeping the Identity of Generic Biopharmaceutical Manufacturers Secret*, HEALTH AFFAIRS WEBLOG, Oct. 16, 2015, http://healthaffairs.org/blog/2015/10/16/who-makes-this-drug-disclosing-the-identity-of-generic-drug-manufacturers/ (accessed Mar. 16, 2017).

have been quite salient since 2013, the first year of the GDUFA program.[128] We observe that most ANDA holders have relatively small ANDA portfolios, but that there is also a small number of extremely large ANDA parent company sponsors who each hold several hundred approved ANDAs. This suggests a landscape with a somewhat bifurcated industry structure—a large number of sponsors having very small portfolios coexisting with a small number of behemoth ANDA portfolio holders. However, we do not as of now have a good sense of how this has been changing over time—the September 2017 publication by FDA of ANDA holders described above reflects only a single cross-section.

With FDA publication of foreign and domestic API, FDF, and contract manufacturing facilities, industry observers are now able to determine whether the recent but steady shift away from domestic and toward foreign manufacturing facilities is continuing or accelerating. Publication of ownership geography might also offer some clues in how the possible rescinding or renegotiation of international trade agreements such as the Trans-Pacific Partnership Agreement might affect the supply of generic prescription drugs available at low cost in the US. Current congressional tax reform efforts may also result in treating Puerto Rico as foreign for import tax purposes, and/or may result in geographical changes in the location of manufacturing facilities.

A limitation of the manufacturing and sponsor statistics reported here is that they are based primarily on aggregate FDA data. We believe two more detailed analyses are of particular regulatory and economic interest. First, while the published data suggest that API and FDF manufacturing facilities of generic drugs are on balance exiting the US and to a much smaller extent from foreign sites, we do not know if similar patterns are occurring for branded drugs. For foreign sites, it would also be useful to quantify the country- and region-specific entry and exit of API and FDF facilities, and where possible relate the generic drug globalization and offshoring trends to those of other manufacturing industries. For domestic sites, it would be instructive to have a Puerto Rico and regional mainland or even state-specific exit and entry analysis, comparing the changing geographical patterns (such as those in the 'rust belt') of the US generic drug industry with other US manufacturing industries.

Second, the data analysed here do not focus on data disaggregated by therapeutic class, formulation (oral, injectable, other), or molecule, nor do they provide economic information on utilization and sales. This type of more disaggregated data is necessary to undertake an economic analysis of competition among molecules and formulations, the concentration among competitors, competitive differences across therapeutic classes, and perhaps most important of all, factors affecting the pricing of generic prescription drugs. These limitations could fruitfully be the focus of future research on the structure, conduct, and performance of the US generic drug industry.[129]

[128] Some limited data on ANDA holders for FY 2013 through FY 2015 have recently been published. See Ke Dong et al., *Economic Impacts of the Generic Drug User Fee Act Fee Structure*, 20 VALUE HEALTH 792–798 (2017).

[129] Research on some of these issues is discussed in Ernst R. Berndt et al., *The Landscape of U.S.; Generic Prescription Drug Markets, 2004-2016* (National Bureau of Economic Research, Working Paper No. 23640), July 2017, http://www.nber.org/papers/w23640 (accessed Feb. 27, 2018).

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