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CONSOLIDATION AND INNOVATION IN THE PHARMACEUTICAL INDUSTRY: THE ROLE OF MERGERS AND ACQUISITIONS IN THE CURRENT INNOVATION ECOSYSTEM

JOANNA SHEPHERD¹

Recent changes in the pharmaceutical industry have spurred an unprecedented wave of mergers and acquisitions. Some researchers and agencies have questioned whether pharmaceutical consolidation could impede drug innovation. However, as I explain in this Article, these concerns are largely based on an outdated understanding of the drug innovation ecosystem. Whereas a few decades ago almost all drug discovery took place inside traditional pharmaceutical companies, today most drug innovation is externally-sourced from biotech companies and smaller firms. Internal R&D is no longer the primary source, or even an important source, of drug innovation. As a result, analyses that focus on the impacts of pharmaceutical consolidation on internal drug innovation are incomplete and missing the point. Instead, merger analyses should examine whether consolidation increases demand for externally-sourced innovation and, ultimately, strengthens aggregate drug innovation.

INTRODUCTION

The pharmaceutical industry has undergone significant changes in recent decades. Intensifying competition from generics, expanding power of pharmaceutical payors, increasing costs of drug development, and growing risks of commercial failure have increasingly strained drug makers' finances. Many firms have responded by consolidating to either reduce costs or create new sources of revenue. As a result, the number of mergers and acquisitions (M&A) in the pharmaceutical industry has recently hit an all-time high. The total value of pharmaceutical M&A deals reached its highest point ever in 2015, and annual deal value is consistently at least double the deal value from a decade ago.

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The increasing pharmaceutical M&A activity has produced a corresponding level of concern about the impacts of consolidation on the industry. While mergers are typically and understandably scrutinized for harm to *competition*, researchers and regulatory agencies occasionally raise less-traditional concerns about harm to *innovation*. These concerns are premised on the idea that, by merging existing competitors into one firm, consolidation will reduce incentives to develop new products in the future. These concerns have been expressed in several recent academic studies that find a negative relationship between pharmaceutical consolidation and innovation activities within the newly-consolidated firm. In a similar vein, both U.S. and European lawmakers are currently scrutinizing proposed mergers in the agricultural industry— between Monsanto and Bayer and Dow and Dupont—in part based on innovation concerns.

However, concerns about the impact of consolidation on drug innovation are largely based on an outdated understanding of the innovation ecosystem in the pharmaceutical industry. Today, most drug innovation originates not in traditional pharmaceutical companies, but in biotech companies and smaller firms, where a culture of nimble decision-making and risk-taking facilitates discovery and innovation. In the later stages of the drug development process, the biotech companies routinely partner with large pharmaceutical companies to advance through expensive late-stage clinical trials and to effectively manufacture, market, and distribute the drugs. In this current ecosystem, biotech and pharmaceutical firms are each able to specialize in what they do best, bringing expertise and efficiencies to the innovation process. The specialization has led to an environment in which approximately three-fourths of new drugs are externally-sourced. Internal R&D is no longer the primary source, or even an important source, of drug innovation in large pharmaceutical companies.

As a result, analyses that focus on mergers' impacts on internal R&D and innovation are missing the point. Instead, proper analyses of the impacts of consolidation on innovation should focus on whether consolidation enables firms to better support aggregate drug innovation in the current ecosystem. Concerns about harm to innovation could be relevant in specific mergers or acquisitions if the consolidating firms are the primary innovators in the area, the firms innovate internally, and there are essentially no sources of external innovation. However, such scenarios are increasingly rare in the current ecosystem. As long as there is sufficient market competition so that firms must innovate to ensure their future profitability and market share, consolidation will often allow firms to devote more resources to externally-sourced innovation. The increased demand for externally-sourced innovation will, in turn, spur incentives to innovate in biotech and small companies. Indeed, data suggests that consolidation is associated with increases in aggregate innovation. In recent years, aggregate innovation has held strong notwithstanding dramatic increases in M&A activity; in fact, 2014 and

2015 generated both record numbers of new drug approvals and record pharmaceutical M&A.

Therefore, merger analyses that focus on the impact of consolidation on internal innovation are incomplete because they fail to recognize that consolidation can increase demand for externally-sourced innovation and, ultimately, strengthen aggregate drug innovation. This Article proceeds as follows. In Section II, I describe the forces that have dramatically changed the pharmaceutical industry's economic environment and driven many firms to consolidate. I also explain the concerns, raised by both researchers and regulatory agencies, about consolidation's potential harm to innovation. In Section III, I explain the current drug innovation ecosystem, detailing the strengths of both traditional pharmaceutical companies and smaller, biotech firms in drug discovery. In Section IV, I argue that proper analyses of mergers must focus not on the impacts to internal R&D, but on the impacts to externally-sourced R&D and aggregate drug innovation. I conclude in Section V.

I. CONSOLIDATION IN THE PHARMACEUTICAL INDUSTRY

Mergers and acquisitions play an important role in pharmaceutical companies' efforts to improve efficiency and add new markets, innovative drugs, and novel technologies. Pharmaceutical M&A has recently hit an all-time high. In 2015, 236 biopharma M&A deals were closed worldwide, with a combined value of over \$403 billion, a new record for the industry.² Although 2016 saw a decrease in combined deal value,³ M&A activity is still up substantially; the annual deal value is now consistently more than twice the average annual deal value in the decade prior to 2014.⁴ Moreover, many commentators predict a pharmaceutical merger boom in the next few years as the Republican control of government brings a more positive outlook for the industry.⁵

2. DELOITTE, 2017 GLOBAL LIFE SCIENCES OUTLOOK: THRIVING IN TODAY'S UNCERTAIN MARKET 20 (2017), <https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2017-life-sciences-outlook.pdf>; Joanne Finnegan, *2015 Was a Record Breaker for M&A in Pharma, Medical and Biotech with Deals Worth \$575 Billion*, BIOSPACE (Jan. 14, 2016), <http://www.biospace.com/News/2015-was-a-record-breaker-for-ma-in-pharma-medical/405749>.

3. MERGERMARKET, PHARMA, MEDICAL, & BIOTECH TREND REPORT: Q1-Q4 2016 2 (2017), <http://www.mergermarket.com/pdf/MergermarketTrendReport.Q1-Q42016.Pharma,Medical,Biotech.pdf>.

4. ERNST AND YOUNG, EY M&A OUTLOOK AND FIREPOWER REPORT 2017 3-4 (2017), [http://www.ey.com/Publication/vwLUAssets/ey-ma-outlook-and-firepower-report-2017/\\$FILE/ey-ma-outlook-and-firepower-report-2017.pdf](http://www.ey.com/Publication/vwLUAssets/ey-ma-outlook-and-firepower-report-2017/$FILE/ey-ma-outlook-and-firepower-report-2017.pdf); IMAP, GLOBAL M&A REPORT: PHARMA/BIOTECH 2016 4 (2016), <http://www.imap.com/Reports/Global%20Pharma%20Biotech%20MA%20Report%202016.pdf>.

5. Reuters, *Donald Trump's Presidency Could Unleash a Pharma Merger Boom*, FORTUNE (Nov. 11, 2016), <http://fortune.com/2016/11/11/donald-trump-pharma-merger-boom/>.

A. Factors Driving Consolidation

Pharmaceutical consolidation has largely been the response to industry-wide shocks that have dramatically changed the landscape of the industry over the last few decades. The aggregate impact of these shocks, discussed in more detail below, has been to squeeze pharmaceutical firms' revenues while increasing their costs. As the shocks have increasingly put firms under economic stress, many have responded by consolidating to either reduce costs or create new sources of revenue.

Many firms have entered into M&A deals as a defensive strategy to offset losses in market share and achieve cost savings.⁶ Evidence has shown that consolidation has enabled many merging firms to streamline operations and eliminate excess capacity resulting from rapidly changing industry conditions.⁷ Others have merged hoping to increase revenues by strengthening existing product portfolios, filling pipeline gaps, entering new therapeutic categories or markets, or acquiring innovative technologies.⁸ Indeed, empirical studies show that firms with an aging portfolio of patented drugs are more likely to merge in order to improve future revenue prospects.⁹

Since the early 1980s, the economic environment facing pharmaceutical companies has changed dramatically, with intensifying competition from generics, expanding power from PBMs, increasing costs of R&D, and growing risk of commercial failure. These changes brought increasing pressure on pharmaceutical firms to lower prices even though, at the same time, many of the firms' costs were increasing.¹⁰ The following discussion briefly explains these changes.

1. Intensifying Generic Competition

First, the nature of competition in the pharmaceutical industry has changed dramatically as brand companies have lost significant market share to generics. The generic industry exploded after the Hatch-Waxman Act in 1984 created an

6. Henry Grabowski, *The Evolution of the Pharmaceutical Industry Over the Past 50 Years: A Personal Reflection*, 18 INT'L. J. OF THE ECON. OF BUS. 161, 173 (2011).

7. David J. Ravenscraft & William F. Long, *Paths to Creating Value in Pharmaceutical Mergers*, in MERGERS AND PRODUCTIVITY 287, 322 (Steven N. Kaplan ed., 2000).

8. Henry Grabowski & Margaret Kyle, *Mergers and Alliances in Pharmaceuticals: Effects On Innovation and R&D Productivity*, in THE ECON. OF CORP. GOVERNANCE AND MERGERS 262, 268–69 (Klaus Gugler & B. Bursin Yurtoglu eds., 2008).

9. Matthew J. Higgins & Daniel Rodriguez, *The Outsourcing of R&D Through Acquisition in the Pharmaceutical Industry*, 80 J. FIN. ECON. 351, 352 (2006); see Patricia M. Danzon ET AL., *Mergers and Acquisitions in the Pharmaceutical and Biotech Industries*, 28 MANAGERIAL AND DECISION ECON. 307, 325 (2007) (explaining study findings that mergers among large firms are often in response to excess capacity due to anticipated patent expirations and gaps in a company's product pipeline).

10. A similar, but more in-depth discussion of these changes can be found in: Joanna Shepherd, *The Prescription for Rising Drug Prices: Competition or Price Controls?*, HEALTH MATRIX: J. OF L. MED. (2017), <https://scholarlycommons.law.case.edu/cgi/viewcontent.cgi?article=1609&context=healthmatrix>.

abbreviated regulatory process that encouraged companies to produce and market cheaper, generic drugs.¹¹ Generics have been further aided by drug substitution laws in every state that allow, or even require, pharmacists to automatically substitute a generic-equivalent drug when a patient presents a prescription for a brand drug.¹² These regulatory changes have allowed generics to capture significant market share from brand companies. Whereas generics comprised only 19 percent of all drugs dispensed prior to 1984, they now represent over 88 percent of prescriptions filled.¹³

The success of generic drugs can be attributed entirely to their lower prices. When a brand drug's patent expires, generics initially enter the market at a price that is, on average, 50 percent less than their brand counterpart.¹⁴ As the months

11. Drug Price Competition and Patent Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984); U.S. CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY, ix (1998), <https://www.cbo.gov/sites/default/files/105th-congress-1997-1998/reports/pharm.pdf>. To spur the introduction of low-cost generics, Hatch-Waxman created the Abbreviated New Drug Application (ANDA) process that allows a generic that demonstrates bioequivalence to rely on *previously submitted* brand-name safety and efficacy data. 21 U.S.C. § 355(j) (2017); *Abbreviated New Drug Application (ANDA): Generics*, FDA (last updated Feb. 27, 2007), <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/>. This greatly truncated process enables generic manufacturers to quickly enter the market after the brand drug's patent expires. Moreover, Hatch-Waxman actively incentivizes generic companies to challenge brand patents' validity by creating a pathway for such challenges and by offering a lucrative incentive to the first generic manufacturer that files an ANDA claiming that the brand patent is either invalid or will not be infringed by the new generic. See U.S. DEP'T HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: 180-DAY GENERIC DRUG EXCLUSIVITY UNDER THE HATCH-WAXMAN AMENDMENTS TO THE FEDERAL FOOD, DRUG, & COSMETIC ACT 1-2 (1998), <http://www.fda.gov/downloads/Drugs/. . ./Guidances/ucm079342.pdf>. If the generic company wins or settles the patent litigation, it receives a 180-day exclusivity period during which the FDA will not approve any other generic versions of the drug, a period in which the first generic can earn substantial profits by shadow pricing the innovator's price. *Id.*

12. BUREAU OF CONSUMER PROT., FTC, DRUG PRODUCT SELECTION 155 (1979).

12. U.S. GOV'T ACCOUNTABILITY OFFICE, DRUG PRICING: RESEARCH ON SAVINGS FROM GENERIC DRUG USE 2 (2012), <http://www.gao.gov/assets/590/588064.pdf>; IMS INSTITUTE FOR HEALTHCARE INFORMATICS, DECLINING MEDICINE USE AND COSTS: FOR BETTER OR WORSE? A REVIEW OF THE USE OF MEDICINES IN THE UNITED STATES IN 2012 15 (May 2013), <http://static.correofarmaceutico.com/docs/2013/05/20/usareport.pdf>; PHRMA, CHARTPACK: BIOPHARMACEUTICALS IN PERSPECTIVE 56 (2015), <http://www.phrma.org/sites/default/files/pdf/chartpack-2015.pdf>.

13. U.S. GOV'T ACCOUNTABILITY OFFICE, DRUG PRICING: RESEARCH ON SAVINGS FROM GENERIC DRUG USE 2 (2012), <http://www.gao.gov/assets/590/588064.pdf>; IMS INSTITUTE FOR HEALTHCARE INFORMATICS, DECLINING MEDICINE USE AND COSTS: FOR BETTER OR WORSE? A REVIEW OF THE USE OF MEDICINES IN THE UNITED STATES IN 2012 15 (May 2013), <http://static.correofarmaceutico.com/docs/2013/05/20/usareport.pdf>; PHRMA, CHARTPACK: BIOPHARMACEUTICALS IN PERSPECTIVE 56 (Spring 2015), <http://www.phrma.org/sites/default/files/pdf/chartpack-2015.pdf>.

14. IMS INSTITUTE FOR HEALTHCARE INFORMATICS, PRICE DECLINES AFTER BRANDED MEDICINES LOSE EXCLUSIVITY IN THE U.S. 2-3 (2016), <https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/PhRMA%20Generic%20Price%20Brief%20January%202016.pdf>.

pass and more generics enter the market, the generic price eventually drops to 80 percent off the pre-expiry brand drug's price. Generic companies are able to charge these lower prices while earning substantial profits because they face significantly lower development and marketing costs than brand drug companies. In contrast to brand companies that spend an average of \$2.6 billion on R&D and the FDA approval process, bringing a new generic drug to market costs only \$1 to \$2 million.¹⁵ In addition, whereas brand companies spend millions of dollars marketing their drugs to physicians and patients,¹⁶ generic companies typically spend very little on marketing, instead relying on automatic substitution laws for the vast majority of their sales. With these significantly lower costs, generic companies can afford to charge a lower price for their drugs and still earn impressive profits.

The lower prices induce many brand drug customers to switch to the lower-priced generics as they enter the market, swiftly eroding brand drugs' market share. Upon market entry, generics now routinely capture over 70 percent of the brand drug's market share within only 3 months of generic entry, and over 80 percent within 12 months.¹⁷ This swift erosion of market share means that many brand pharmaceutical firms experience dramatic decreases in revenue after they reach the "patent cliff" and generics enter the market. An early study by the U.S. Congressional Budget Office found that during the first decade after the Hatch-Waxman Act, total net revenues generated by new drugs declined by 12 percent as a result of generic entry.¹⁸ Between 2012 and 2018, it is estimated that pharmaceutical companies will lose almost \$150 billion in revenues because of generic entry after patent expirations.¹⁹

15. 15.CHARTPACK: BIOPHARMACEUTICALS IN PERSPECTIVE, *supra* note 13, at 36; OFFICE OF THE ASSISTANT SEC'Y FOR PLANNING & EVALUATION, U.S. DEP'T OF HEALTH & HUMAN SERVS., EXPANDING THE USE OF GENERIC DRUGS 4-5 (Dec. 1, 2010), <https://aspe.hhs.gov/system/files/pdf/76151/ib.pdf>; Henry Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, 8 GEORGETOWN PUB. POLICY REV. 7, 13 (2003) (noting that "[g]eneric firms can file an Abbreviated New Drug Application (ANDA), a process that takes only a few years and typically costs a few million dollars).

16. Brand companies spent between \$103 million and \$249 million on the top-10 most heavily advertised drugs in 2014 alone. See Beth Snyder Bulik, *The Top-10 Most Advertised Prescription Drug Brands*, FIERCEPHARMA (2015), <http://www.fiercepharma.com/special-report/top-10-most-advertised-prescription-drug-brands> (last accessed Mar. 27, 2017).

17. See PHARMA, CHARTPACK: PHARMACEUTICALS IN PERSP. 57 (2015), <http://www.phrma.org/sites/default/files/pdf/chartpack-2015.pdf> (showing that the average lifetime revenue for drugs introduced between 1991 and 2005 rose from \$3.4 billion to \$5.1 billion, then fell to \$2.9 billion for drugs introduced between 2005 and 2009).

18. U .S. CONG. BUDGET OFF., ISSUES IN DESIGNING A PRESCRIPTION DRUG BENEFIT FOR MEDICARE 38 (2002).

19. PRICEWATERHOUSECOOPERS, FROM VISION TO DECISION: PHARMA 2020, 6 (2012), <http://www.pwc.com/gx/en/pharma-life-sciences/pharma2020/assets/pwc-pharma-success-strategies.pdf>.

2. *Expanding Power of Pharmacy Benefit Managers*

Second, brand companies have also faced increased power from pharmaceutical “payors.” Pharmacy benefit managers (PBMs), which administer the prescription drug coverage for over 95 percent of insured Americans,²⁰ have adopted various benefit changes and tools to reduce pharmaceutical prices and steer patients to less-expensive alternatives.²¹ For example, PBMs have successfully reduced drug spending by requiring substitution of generic drugs for brand name drugs when clinically appropriate.²² PBMs also employ tiered formularies—a list of approved or preferred drugs for the health plan—and steer consumers to the formulary drugs with incentives such as lower copayments. Because formulary status can greatly influence the sales of a drug, PBMs are able to negotiate significant discounts from brand drug manufacturers in exchange for a formulary listing.²³

These and other innovative tools have saved Americans billions of dollars each year.²⁴ However, they have also dramatically changed the landscape of the pharmaceutical market by lessening drug companies’ influence over prices. In the 1970s, most prescription drugs were prescribed by doctors that were largely insensitive to price, methodically filled by pharmacists, and paid for by consumers or third-party payors that had little influence over the drug chosen or the price paid.²⁵ As a consequence, drug manufacturers had enormous control over price. In contrast, the market for prescription drugs today is one in which the PBMs and drug plans have harnessed the buying clout of millions of consumers to negotiate discounted prescription drug prices.²⁶ PBMs and drug plans now largely determine what consumers pay for drugs, which pharmacies they use, and which drugs they take.²⁷ As a result, PBMs and drug plans have

20. Letter from Fed. Trade Comm’n to Senator Richard L. Brown, N.D. Senate 4 (Mar. 8, 2005), <http://www.ftc.gov/os/2005/03/050311northdakotacomnts.pdf>.

21. See Dan P. Goldman, Geoffrey F. Joyce, & Yuhui Zheng, *Prescription Drug Cost Sharing: Associations With Medication and Medical Utilization and Spending and Health*, 298 J. AM. MED. ASS’N 61, 61 (2007) (describing “mail-order pharmacies, mandatory generic substitution, coinsurance plans, and multi-tiered formularies”).

22. U.S. GOV’T. ACCOUNTABILITY OFFICE, EFFECTS OF USING PHARMACY BENEFIT MANAGERS ON HEALTH PLANS, ENROLLEES, AND PHARMACIES 4 (2003).

23. Letter from Fed. Trade Comm’n to Greg Aghazarian, California General Assembly, 6–7 (Sept. 7, 2004), <http://www.ftc.gov/be/V040027.pdf> (stating how PBMs can substitute for generic drugs and enter into contracts with pharmaceutical manufacturers to lower costs).

24. U.S. CONG. BUDGET OFFICE, *supra* note 18, at 38 (estimating the magnitude of PBMs’ cost-savings at approximately 30 percent of total prescription drug spending); VISANTE, PHARMACY BENEFIT MANAGERS (PBMS): GENERATING SAVINGS FOR PLAN SPONSORS AND CONSUMERS 6 (2016) (predicting that the PBM tools will save nearly \$654 billion).

25. Grabowski, *supra* note 6, at 167.

26. Thomas Gryta, *What is a ‘Pharmacy Benefit Manager’?*, WALL STREET J. (July 21, 2011), <http://online.wsj.com/article/SB10001424053111903554904576460322664055328.html> (stating how Pharmacy Benefit Manager contracts with drug manufacturers include cost-cutting incentives).

27. *Id.* (explaining how Pharmacy Benefit Managers aid in drug-related decisions).

replaced drug manufacturers in the driver's seat when it comes to determining prices.

In addition to influencing prices, PBMs are keeping an increasing share of the total expenditures on pharmaceuticals. Today, brand manufacturers receive only 39 percent of the gross national spending on drugs.²⁸ Forty-two percent of gross spending is captured by PBMs, health plans, and supply-chain entities, such as pharmacies and wholesalers.²⁹ Brand manufacturers' share of total drug spending has steadily declined as the buying clout of PBMs and drug plans has increased.³⁰

3. *Increasing Costs and Risks of Product Development*

Third, while facing increased competition from generics and pressure to reduce prices from PBMs, drug companies have also experienced significant increases in both the costs of drug development and the risks of product failures. Since the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act, the FDA has continued to increase the requirements for new drug approvals. For example, whereas clinical trials in the 1970s typically enrolled only 2,000 patients, trials in the 1990s regularly enrolled over 5,000 patients.³¹ Similarly, the costs of recruiting patients, the length of the clinical trial period, and the number and complexity of clinical tests used in clinical trials have increased over time.³² These more stringent requirements, along with the more complex science associated with specialized medications, have significantly increased the costs of drug development and FDA approval and in turn lengthened the time to market, driving up the cost of investment. The most current estimates indicate that it now costs approximately \$2.6 billion to develop and bring each new drug to market.³³ Those costs were estimated to be only \$179 million in the 1970s,³⁴ \$413 million

28. AARON VANDERVELDE AND ELEANOR BLALOCK, THE PHARMACEUTICAL SUPPLY CHAIN: GROSS DRUG EXPENDITURES REALIZED BY STAKEHOLDERS 4, BERKLEY RES. GROUP. (2017) http://www.thinkbrg.com/media/publication/863_Vandervelde_PhRMA-January-2017_WEB-FINAL.pdf.

29. *Id.*

30. *Id.* at 6.

31. Grabowski, *supra* note 6 at 169.

32. *See id.* at 170 (showing the increase in costs over time); *see also* PHRMA, BIOPHARMACEUTICAL RES. & DEVELOPMENT: THE PROCESS BEHIND NEW MEDICINES 9 (2015) (discussing various factors and challenges that have become more prevalent in current drug development).

33. JOSEPH A. DIMASI, *in* TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, BRIEFING: COST OF DEVELOPING A NEW DRUG (Nov. 18, 2014) *available at* http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18_2014.pdf (last accessed May 2, 2017).

34. *See* Grabowski, *supra* note 6 at 170 (providing the number adjusted for inflation in "constant 2000 dollars").

in the 1980s,³⁵ and \$900 million in the 1990s and early 2000s.³⁶ In contrast, it costs generic manufacturers only one to two million dollars to bring a drug to market.³⁷

Moreover, only about ten percent of brand drugs that begin clinical trials are eventually approved by the FDA. The most recent study to track FDA approval rates found that the approval rate varied by trial phase: phase I had a 64.5% success rate, phase II had a 32.4% success rate, phase III had a 60.1% success rate, and the FDA approved 83.2% of applications that passed phase III.³⁸ Ultimately, of 100 drugs that begin Phase I trials, only ten drugs will eventually be approved.³⁹ Thus, despite dramatic increases in research and development (R&D) spending, drug approval rates have increased little in recent decades.⁴⁰

Even after FDA approval, pharmaceutical manufacturers increasingly face patent challenges that reduce the likelihood that drugs will achieve commercial success. Hatch-Waxman actively incentivizes generic companies to challenge the validity of brand-name patents by creating a pathway for such challenges and by offering a lucrative incentive to the first generic manufacturer that files a challenge claiming that the brand patent is either invalid or will not be infringed by the new generic (known as a Paragraph IV challenge).⁴¹ If the generic company wins or settles the patent litigation, it receives a 180-day exclusivity period during which the FDA will not approve any other generic versions of the drug, a period in which the first generic can earn substantial profits.⁴² Paragraph

35. *Id.* (citing Joseph A. DiMasi ET AL., *Cost of Innovation in the Pharmaceutical Industry*, 10 J. HEALTH ECON. 107 (1991)).

36. Joseph A. DiMasi, Ronald W. Hansen, & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180 (2003).

37. OFFICE OF THE ASSISTANT SEC'Y FOR PLANNING & EVALUATION, U.S. DEP'T OF HEALTH & HUMAN SERVS., EXPANDING THE USE OF GENERIC DRUGS 4–5 (Dec. 1, 2010), <http://aspe.hhs.gov/basic-report/expanding-use-generic-drugs#11>.

38. Michael Hay ET AL., *Clinical Development Success Rates for Investigational Drugs*, 32 NATURE BIOTECHNOLOGY 40, 41 (2014). (Discussing how, “Phase I trials...focus on the safety of the drug and determine the metabolic and pharmacologic actions of drugs, side effects of increasing doses, and early evidence of effectiveness. Phase II trials...focus on the drug’s effectiveness. Phase III verifies the drug’s efficacy and safety with 1,000-3,000 subjects suffering from the disease...”).

39. *Id.*

40. See PHRMA, ANNUAL MEMBERSHIP SURVEY 4 (2015), http://www.phrma.org/sites/default/files/pdf/2015-phrma_profile_membership_results.pdf (showing new drug approvals have not increased at the same pace as R&D spending); See also *Summary of NDA Approvals and Receipts: 1938 to the Present*, FDA (last updated Jan. 18, 2013), <http://www.fda.gov/aboutfda/whatwedo/history/productregulation/summaryofndaapprovalsreceipts1938tothepresent/default.htm> (showing how the rising costs of R&D do not correlate to a growth in approval ratings).

41. See Margo Bagley, *Patent Term Restoration and Non-Patent Exclusivity in the U.S. in Pharmaceutical Innovation, Competition, and Patent Law*, 116–117, (2013) (making note of the costs of litigation and effects on the drug that patent challenges have).

42. U.S. DEP'T HEALTH & HUM. SERVS, *supra* note 37, at 2. (showing how the company that wins or settles a patent litigation case gets a 180-day exclusivity period).

IV challenges have exploded in recent years; whereas only 9 percent of drugs facing generic entry in 1995 were challenged, 81 percent of drugs facing generic entry in 2012 were challenged.⁴³ Moreover, Paragraph IV challenges are occurring earlier in the life of brand drugs. Drugs entering the market as generics in 1995 faced their first challenge 18.7 years after original launch.⁴⁴ By comparison, drugs entering the market as generics in 2012 saw only 6.9 years between market launch and the first Paragraph IV challenge.⁴⁵ These challenges threaten a drug's commercial success and cost pharmaceutical companies significant legal fees.⁴⁶

Moreover, the Leahy-Smith America Invents Act in 2012 gave generics a new administrative venue to challenge patents, the *inter partes review* (IPR).⁴⁷ In contrast to Hatch-Waxman litigation that occurs in federal district court, IPR proceedings culminate in a trial before the Patent Trial and Appeal Board (PTAB) of the U.S. Patent and Trademark Office. IPR was expected to offer a more efficient and less costly alternative to Hatch-Waxman's litigation pathway, but important differences between PTAB trials and district court litigation create significant advantages for generic patent challengers.⁴⁸ The PTAB applies a lower standard of proof for invalidity than do district courts in Hatch-Waxman litigation.⁴⁹ It is also easier to meet the standard⁵⁰ of proof in a PTAB trial because there is a more lenient claim construction standard and a substantially limited ability to amend patent claims.⁵¹ Moreover, on appeal, PTAB decisions

43. Henry Grabowski, Genia Long, & Richard Mortimer, *Recent Trends in Brand-Name and Generic Drug Competition*, 17 J. MED ECON. 207, 211 (2014).

44. *Id.* at 212.

45. *Id.*

46. *Id.* (noting that for high revenue drugs, generics may be quick to initiate litigation because there is a large potential return on investment compared to the cost of litigation).

47. See Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 299-305 (2011) (setting forth the ability to have an IPR instead of a trial for patent challenges).

48. See generally Joanna Shepherd, *Disrupting the Balance: The Conflict between Hatch-Waxman and Inter Partes Review*, 6 NYU J. INTELLECTUAL PROP. & ENTMT'L 14, 28, 33 (2016) (explaining that brand drugs are better protected by Hatch-Waxman due in part to venue and that statutory requirements that require IPR claims be decided within twelve to eighteen months create an environment where patent challengers have unprecedented ability to attack patents).

49. See *Microsoft Corp. v. i4i Ltd.*, 564 U.S. 91, 95 (2011) (holding that a clear and convincing showing of invalidity is required to invalidate patents); 35 U.S.C. § 316(e) (2012) (establishing a "preponderance of the evidence" standard in IPR proceedings).

50. See *Cuozzo Speed Tech. LLC v. Lee*, 136 S. Ct. 2131, 2144-5 (2016) (providing that the "use of the broadest reasonable construction standard increases the possibility that the examiner will find the claim too broad (and deny it)... a standard that district courts do not apply").

51. U.S. PAT. & TRADEMARK OFF., *Patent Trial and Appeal Board Motion to Amend Study*, at 3-4 (Apr. 30, 2016), <https://www.uspto.gov/sites/default/files/documents/2016-04-30%20PTAB%20MTA%20study.pdf>; but see <http://www.finnegan.com/files/Publication/c8ee3013-3e31-4358-8399-6986df1a51ba/Presentation/PublicationAttachment/e6715d28-f2e8-403d-a43d-6e1f79881348/15-1177%2008-16-16.pdf> (granting en banc review regarding whether the PTO can require the patent owner to bear the burden of persuasion regarding patentability of amended claims).

in IPR proceedings are given more deference than district court decisions.⁵² Finally, while patent challengers in district court must establish sufficient Article III standing, IPR proceedings do not have a standing requirement, allowing any member of the public other than the patent owner to initiate an IPR challenge.⁵³ These advantages for patent challengers have led to significantly different patent invalidation rates in PTAB trials compared to rates in district court litigation.⁵⁴ Whereas patents challenged in district court are invalidated in less than 40%⁵⁵ of cases, IPRs have resulted in patent invalidations in a shocking 70% of cases.⁵⁶

The intensifying competition from generics, expanding power of PBMs, escalating R&D costs, and increasing risk of patent challenges mean that many new pharmaceuticals will never attain commercial success. Even for the 10 percent of drugs that receive FDA approval, only 20 percent will ever earn enough revenue to cover the growing R&D costs.⁵⁷ Moreover, the likelihood that a drug will become profitable has decreased over time as both the risk of failure and the costs of development have increased.⁵⁸ The average lifetime revenues for new drugs are lower now than at any point in the last 25 years.⁵⁹ These shocks have put many pharmaceutical firms under significant economic stress, motivating consolidation as a means to streamline costs and provide new sources of revenue.

B. Concerns about Consolidation's Impact on Innovation

The increasing pharmaceutical M&A activity has produced a corresponding level of concern about the impacts of consolidation on the

52. Frederick H Rein ET AL., *Merck & Cie v. Gnosis: A More Deferential Standard of Review for Inter Partes Review Decisions*, 13 J. GENERIC MED. 93, 93 (2017).

53. See Saurabh Vishnubhakat et. al., *Strategic Decision Making in Dual PTAB and District Court Proceedings*, 31 BERKELEY TECH. L.J. 45, 55, n.39 (2016) (citing *Consumer Watchdog v. Wis. Alumni Research Found.*, 753 F.3d 1258 (Fed. Cir. 2014) (explaining how IPR hearings do not have standing requirements while, in comparison, trial court challenges do).

54. Cf. PRICEWATERHOUSECOOPERS, 2016 PATENT LITIGATION STUDY: ARE WE AT N INFLECTION POINT? 11 (2016), <https://www.pwc.com/us/en/forensic-services/publications/assets/2016-pwc-patent-litigation-study.pdf> (illustrating in Figure 9 the vast difference in patent invalidation in PTAB trials in comparison to district court trials).

55. *Id.* at 10 (showing how patent holders win in bench trials over 61% of the time).

56. U.S. Pat. & Trademark Off., Patent Trial and Appeal Board Update 10 (2016), <https://www.uspto.gov/sites/default/files/documents/2016-6-30%20PTAB.pdf>.

57. See also Hay ET AL., *supra* note 38 at 41 (stating that ten percent of applications obtain approval); see also John A. Vernon ET AL., *Drug Development Costs When Financial Risk Is Measured Using the Fama-French Three-Factor Model*, 19 HEALTH ECON. 1002, 1004 (2010) (stating that only about twenty percent of NME brought to market earn enough revenue to cover R&D costs).

58. Ernst Berndt ET AL., *Decline in Economic Returns from New Drugs Raises Questions about Sustaining Innovations*, 34 HEALTH AFF. 245, 250 (2015).

59. See PHARMA, CHARTPACK: PHARMACEUTICALS IN PERSP. 44 (2015), <http://www.phrma.org/sites/default/files/pdf/chartpack-2015.pdf> (showing that the average lifetime revenue for drugs introduced between 1991 and 2005 rose from \$3.4 billion to \$5.1 billion, then fell to \$2.9 billion for drugs introduced between 2005 and 2009).

industry. Competition enforcers have traditionally scrutinized mergers for harms to competition, which can harm consumers by increasing prices and restricting product choice. However, researchers and regulatory agencies occasionally raise less-traditional concerns about harms to innovation. These concerns are premised on the idea that mergers may disrupt “innovation markets”, or markets that consist “of the research and development directed to particular new or improved goods or processes, and the close substitutes for that research and development.”

⁶⁰ Innovation markets exist in industries, such as pharmaceutical and high-tech industries, that depend on rapid technological advancement and place a high value on patented products. Inquiries into the impacts of consolidation on innovation markets stem from the notion that, by merging existing competitors into one firm, consolidation will reduce incentives to develop new products in the future.⁶¹

Concerns that pharmaceutical M&A may reduce innovation have been expressed in several recent academic studies that find a negative relationship between consolidation and “innovation activities” within the newly-consolidated firm. Various studies have found that pharmaceutical mergers have led to lower R&D expenditures in the consolidated firm, as compared to the expenditure in both companies beforehand or to the expenditure in other non-merging companies.⁶² Similarly, studies have found that consolidation leads to a reduction in the number of R&D projects in the consolidated firm.⁶³ Some evidence also suggests that the consolidated firm produces fewer new patents than the two separate firms did before the merger.⁶⁴ However, as acknowledged by the studies themselves, much of the reduction in R&D expenditures, projects in development, and number of new patents in the newly-consolidated firm is the

60. DEP’T. OF JUST. & FED. TRADE COMM’N, ANTITRUST GUIDELINES FOR THE LICENSING OF INTELLECTUAL PROPERTY 10–11 (1995), <https://www.justice.gov/sites/default/files/atr/legacy/2006/04/27/0558.pdf>

61. Douglas L. Wald & Deborah L. Feinsein, *Merger Enforcement in Innovation Markets: The Latest Chapter—Genzyme/Novazyme*, ANTITRUST SOURCE 2 (July 2004), http://www.americanbar.org/content/dam/aba/publishing/antitrust_source/Jul04_Feinsein7_23.authcheckdam.pdf.

62. JUSTUS HAUCAP & JOEL STIEBALE, HOW MERGERS AFFECT INNOVATION: THEORY AND EVIDENCE FROM THE PHARMACEUTICAL INDUSTRY 21 (Hans-Theo Normann, ed.) Düsseldorf University Press (2016), http://www.dice.hhu.de/fileadmin/redaktion/Fakultaeten/Wirtschaftswissenschaftliche_Fakultaet/DICE/Discussion_Paper/218_Haucap_Stiebale.pdf (finding that R&D spending declines post-merger); see also Carmine Ornaghi, *Mergers and Innovation in Big Pharma*, 27 INT’L. J. INDUS. ORG. 70, 76 (2009) (finding R&D expenditures decline after a merger); Danzon ET AL., *supra* note 9, at 322–324 (finding that small merging firms experienced slower growth in R&D expenditures than non-merging firms, but there was no difference for large firms).

63. Ravenscraft & Long, *supra* note 7, at 317 (finding that some mergers resulted in the cancelling, postponing, or delaying of R&D projects).

64. Haucap & Stiebale, *supra* note 62, at 21 (finding that patent stocks decline post-merger); Ornaghi, *supra* note 62, at 76 (finding that number of new patents and number of new important patents decline after a merger).

result of efficiency gains.⁶⁵ Mergers enable firms to streamline duplicative operations, reduce excess capacity, and achieve economies of scale, in turn reducing the consolidated firms' expenses and eliminating redundant projects or patents.⁶⁶ Additionally, studies comparing the innovation activities in newly-merged firms with the activities in non-merging firms likely suffer from selection bias; firms under economic stress are more likely to merge, so a comparison of merging with non-merging firms is capturing differences between firms with different economic prospects.⁶⁷

To escape these confounding influences and selection effects, a recent study has examined the impact of consolidation on innovation activities outside the firm on the theory that a reduction in competition following a merger would reduce competitors' incentives to innovate.⁶⁸ The study found that mergers reduce R&D spending and the number of patents in both the merging firm and in rival firms. However, as I explain in the next section, all firms (including consolidated firms and rivals) have experienced a general decrease in internal R&D activities as they adjust to the new economic reality of the pharmaceutical industry that makes external sourcing of R&D more attractive than internal development. Moreover, consolidation of a rival may compel firms to substitute away from internal R&D even more than the general trend would suggest. Because consolidation typically improves efficiency in the consolidated firm, rival firms may begin to outsource more of their R&D, with a corresponding decrease in their in-house innovation, in an effort to compete with the more efficient consolidated firm.

In addition to the academic research on the impact of M&A on innovation, regulatory agencies have also raised concerns about consolidation's impact on innovation markets. Merger challenges based on the impact of consolidation on innovation are relatively new; the competition agencies did not challenge a merger on the ground that it would harm innovation until the mid-1970s,⁶⁹ and it wasn't until the 1990s that FTC and DOJ began to routinely question the impact of mergers on innovation. During this period, the agencies often required the divestiture or compulsory licensing of intellectual property to approve mergers, especially in pharmaceutical mergers.⁷⁰

65. Ravenscraft & Long, *supra* note 7, at 313, 317.

66. Grabowski, *supra* note 6, at 173; Ravenscraft & Long, *supra* note 7, at 317.

67. Danzon ET AL., *supra* note 9, at 325–326.

68. *SEE HAUCAP & STIEBALE, supra* note 62, at 21 (finding that patent stocks in newly merged entities decline an average of thirty percent immediately post-merger).

69. *See* Complaint at 364, 368, In the Matter of Xerox Corp., 86 F.T.C. 364 (Fed. Trade Comm'n July 20, 1975) (No. 8909) (claiming that Xerox maintained patent barriers and harmed innovation through mergers)

70. *See, e.g.,* Baxter Int'l, 123 F.T.C. 904, 910–911, (1997) (in the merger of Baxter International and Immuno-International, two of the leading commercial developers of the Factor VIII inhibitor treatments used to treat antibodies in hemophilia, FTC required Baxter to divest certain treatment assets);

The agencies' innovation harm claims essentially ceased during the George W. Bush Administration in the 2000s.⁷¹ While the FTC and DOJ pressed innovations concerns in their challenges to 51 mergers during the 1990s,⁷² they pursued an innovation harm claim in only one case between 2004–2008.⁷³ Timothy Muris, FTC Chairman from 2001–2004, explained that the agencies' reluctance to cite innovation harms arose from an uncertainty about the relationship between concentration and innovation: “there is no reason to believe, a priori, that a particular merger is more likely to harm innovation than to help it—which is, of course, simply another way of saying that there is no empirical basis for a presumption.”⁷⁴ Critics of merger enforcement in innovation markets maintained that, instead of reducing innovation, market concentration could increase innovation because market power gave firms both the resources to invest in R&D and the ability to think long-term instead of worrying about short-term responses to rivals. Indeed, during this time, even the Supreme Court noted that market power could increase innovation because the ability to charge monopoly prices “induces risk taking that produces innovation and economic growth.”⁷⁵

However, regulatory agencies have recently expressed a renewed interest in examining the impacts of mergers on innovation. In 2015, the Department of Justice (DOJ) opposed the proposed merger of Applied Materials and Tokyo Electron “to protect competition and future innovation for the development of machinery used to make the memory and logic chips that power smartphones, tablets, computers, and many other products.”⁷⁶ That same year, DOJ opposed the proposed merger of Comcast and Time Warner Cable, even though there was little direct competition between the parties, because the merger would make

see also, e.g., In the Matter of Ciba-Geigy Ltd., 123 F.T.C. 842, 844, 865–67 (1997) (in the merger of Ciba-Geigy and Sandoz, the two leading commercial developers of gene therapy products, FTC required the compulsory licensing of the specified gene therapy technology and patent rights to a competitor that could compete with the combined firm).

71. FED. TRADE COMM'N, ANTITRUST REGULATION OF INNOVATION MARKETS: REMARKS OF J. THOMAS ROSCH 9 (2009), https://www.ftc.gov/sites/default/files/documents/public_statements/antitrust-regulation-innovation-markets/090205innovationspeech.pdf.

72. David A. Balto & Andrew M. Wolman, *Intellectual Property and Antitrust: General Principles*, 43 IDEA 395, 424–25 (2003).

73. FED. TRADE COMM'N *supra*, note 71.

74. *See* Statement of FTC Chairman Timothy J. Muris in the Matter of Genzyme Corporation/Novazyme Pharmaceuticals 23 (2004), <https://www.ftc.gov/system/files/attachments/press-releases/ftc-closes-its-investigation-genzyme-corporations-2001-acquisition-novazyme-pharmaceuticals-inc./murisgenzymestmt.pdf>.

75. *Verizon Comm. Inc. v. Law Off. Of Curtis v. Trinko, LLP.*, 540 U.S. 398, 409 (2004) (suggesting that the mere possession of monopoly power is not unlawful because it induces risk taking).

76. *Statement of Bill Baer, Assistant Attorney General Antitrust Division, Hearing on 'Oversight of the Enforcement of Antitrust Laws' Before the Subcomm. on Antitrust, Competition Policy and Consumer Rights, Comm. on the Judiciary*, at 7 (Mar. 9, 2016) (statement of Bill Baer, Assistant Att'y Gen., Antitrust Division)

“Comcast an unavoidable gatekeeper” for future innovative internet services.⁷⁷ Further, although the proposed merger between Halliburton and Baker Hughes did involve competitive overlap of products and services, DOJ tried to block the merger in 2016 in part because the two companies “drive innovation in these markets, often leading the way in developing next-generation technology to solve the most challenging problems facing the oil and gas industry.”⁷⁸

The European Commission has similarly raised innovation concerns in its analyses of several recent mergers. In 2015, the Commission argued that the merger of Biomet and Zimmer Holdings, two orthopedic implant producers for knees and elbows in the U.S., would have led to “less innovation and choice.”⁷⁹ That same year, the Commission granted the acquisition of GlaxoSmithKline’s oncology business by Novartis conditional on the divestment of two cancer treatments after concluding that, without divestment, the acquisition may have “reduced innovation, with the likely abandonment of Novartis’ broad clinical trial program.”⁸⁰ Similarly, in 2016, the Commission granted the acquisition of mobile network operator BASE by Liberty Global subject to certain divestment requirements because of concerns that the acquisition would otherwise result in “less choice and innovation” for mobile consumers.⁸¹

Several mergers face scrutiny for potential innovation harms in both the U.S. and Europe. Although most contested deals are not based exclusively on innovation markets, claims of innovation harm are increasing and often result in the required divestiture of innovation-related assets. In the agricultural industry, opponents to the proposed merger of Monsanto and Bayer argue that consolidation will slow innovation in crop biotechnology and the development of new seed traits,⁸² with U.S. lawmakers asserting that the consolidated seed

77. *Comcast Corporation Abandons Proposed Acquisition of Time Warner Cable After Justice Department and the Federal Communications Commission Informed Parties of Concerns*, DEP’T OF JUST. (Apr. 24, 2015), <https://www.justice.gov/opa/pr/comcast-corporation-abandons-proposed-acquisition-time-warner-cable-after-justice-department>.

78. *Assistant Attorney General Bill Baer Delivers Remarks at Press Call Announcing that the Justice Department Seeks to block Halliburton’s Acquisition of Baker Hughes*, DEP’T OF JUST. (Apr. 6, 2016), <https://www.justice.gov/opa/speech/assistant-attorney-general-bill-baer-delivers-remarks-press-call-announcing-justice>.

79. European Commission Press Release IP/15/4727, *Mergers: Commission approves acquisition of orthop[edic] implants producer Biomet by Zimmer, subject to conditions* (Mar. 30, 2015) http://europa.eu/rapid/press-release_IP-15-4727_en.htm.

80. European Commission Press Release IP/15/3842, *Mergers: Commission approves acquisition of GSK’s oncology business by Novartis, subject to conditions* (Jan. 28, 2015) http://europa.eu/rapid/press-release_IP-15-3842_en.htm.

81. European Commission Press Release IP/16/241, *Mergers: Commission clears acquisition of mobile network operator BASE by Liberty Global, subject to conditions* (Feb. 4, 2016) http://europa.eu/rapid/press-release_IP-16-241_en.htm.

82. David McLaughlin, *Bayer, Monsanto Face Global Review as Farmer Options Shrink*, *Bloomberg Markets*, BLOOMBERG (Sept. 14, 2016, 7:50 AM), <https://www.bloomberg.com/news/articles/2016-09-14/bayer-monsanto-confront-global-review-as-farmer-options-shrink>.

and crop-chemical giant would have “reduced incentives and ability to innovate.”⁸³ Similarly, the European Commission has raised concerns that the proposed merger between Dow and Dupont, which would create the world’s largest integrated crop protection and seeds company, “may lead to a reduction of innovation in crop protection as a whole.”⁸⁴ U.S. lawmakers have also raised concerns that the Dow-Dupont merger “will reduce incentives to invest in research and development.”⁸⁵

Commentators have expressed concern that the increased scrutiny of innovation markets in the agricultural industry may soon bleed over into the pharmaceutical industry. However, as I discuss in the following section, the innovation ecosystem in the pharmaceutical industry has changed dramatically, making many inquiries of consolidation’s impact on innovation immaterial. Analyses of the impacts of consolidation on innovation must take into account the new reality that most innovation does not occur internally, and consolidation may enable firms to increase both their support of and demand for externally-sourced innovation.

II. THE CURRENT DRUG INNOVATION ECOSYSTEM

Since the advent of modern biotech in the 1970s with the formation of Genentech,⁸⁶ biotech companies have played an increasingly important role in the pharmaceutical industry. Today, about two-thirds of New Molecular Entities (“NMEs”) approved by the FDA originate in biotech and small pharmaceutical companies,⁸⁷ and these companies account for almost 70 percent of the current global pipeline of drugs under development.⁸⁸ Moreover, traditional pharmaceutical companies routinely look to biotech companies as critical external sources of R&D. Indeed, 74 percent of new drugs are originally

83. Press Release, Senator Mike Lee, Lee, Klobuchar React to Proposed Bayer-Monsanto Merger (Sept. 14 2016), <http://www.lee.senate.gov/public/index.cfm/press-releases?ID=E0254B06-5138-474B-A981-36659807DCE4>.

84. European Commission Press Release IP/16/2784, Mergers: Commission opens in-depth investigation into proposed merger between Dow and DuPont (Aug. 11, 2016) http://europa.eu/rapid/press-release_IP-16-2784_en.htm.

85. *Consolidation and Competition in the U.S. Seed and Agrochemical Industry, Before the Judiciary Comm.*, (Sept. 20, 2016) (statement of Mike Lee, Senator for Utah).

86. *See generally*, SALLY SMITH HUGHES, GENETECH: THE BEGINNINGS OF BIOTECH (2011).

87. ULRICH GEILINGER ET AL., TRENDS IN US NEW DRUG APPROVALS 12 (2016), <http://www.hbmpartners.com/wAssets/docs/industry-reports/HBM-Report-Trends-in-US-New-Drug-Approvals-2006-2015.pdf>.

88. DAVID THOMAS & CHAD WESSEL, EMERGING THERAPEUTIC COMPANY INVESTMENT AND DEAL TRENDS 30 (June 2016).

developed externally, and later obtained by a pharmaceutical company through a merger, acquisition, licensing deal, or other alliance.⁸⁹

In the pharmaceutical industry, biotech companies are generally smaller companies that are primarily focused on research and development to identify molecules to be used in new drug products.⁹⁰ Whereas pharmaceutical companies have typically focused on the development of traditional chemically-synthesized drugs, biotech companies are usually focused on applying biotechnology to produce drugs from living cells.⁹¹ After the identification of promising molecules, biotech companies often license or sell the rights to the future drug, or form some other sort of partnership with a traditional pharmaceutical company that markets and distributes the drug.⁹² These traditional pharmaceutical companies are generally larger than biotech companies and, though also involved in research and development, devote significant efforts to the clinical testing, marketing, manufacturing, and distribution of drugs.⁹³

A. The Evolution of Pharmaceutical Innovation

Several forces in the 1970s and 1980s combined to bring about the rapid growth in the biotech industry. First, revolutionary breakthroughs that took place in universities in the 1970s, such as gene splicing and the ability to create antibodies that specifically target certain antigens, elevated the importance of industry-university connections and accelerated the pace of discovery in biomedical sciences.⁹⁴ Second, changes in financial regulations and tax law led

89. MURRAY AITKEN & MICHAEL KLEINROCK, LIFETIME TRENDS IN BIOPHARMACEUTICAL INNOVATION 4 (Jan. 2017) https://www.statnews.com/wp-content/uploads/2017/01/Lifetime_Trends_in_Biopharmaceutical_Innovation.pdf.

90. Mark Terry, *Biotech vs. Big Pharma: Which is the Better Place to work?*, BIOSPACE (Sept. 9, 2016), <http://www.biospace.com/News/biotech-vs-big-pharma-which-is-the-better-place-to/432908>.

91. Michelle Ahern, *The Difference Between Pharmaceutical and Biotechnology*, MORGAN MCKINLEY (Sept. 12, 2016), <https://www.morganmckinley.ie/article/difference-between-pharmaceutical-and-biotechnology>.

92. See Ulrich Geilinger ET AL., *Trends in US New Drug Approvals*, 12 (2016) <http://www.hbmpartners.com/wAssets/docs/industry-reports/HBM-Report-Trends-in-US-New-Drug-Approvals-2006-2015.pdf>, (demonstrating how the “majority of new drug approved by FDA in 2015 (and the years before) originated at smaller companies (i.e. companies outside of the largest 30 biopharma companies). As these smaller companies often out-license their drug candidates or get acquired before approval, the number of approvals in their name (16 in 2015) understates their important contribution to the development of new drugs...”).

93. *Id.* at 11 providing that large pharmaceutical companies developing drugs purchased through company acquisition, continue to develop drugs in-house.; see generally, Richard Anderson, *Pharmaceutical Industry Gets High on Fat Profits*, BBC (Nov. 6, 2014)(summarizing data gathered by GlobalData, a large data collection and analysis firm, which demonstrates that big pharma’s spending on sales and marketing greatly outweighs money spent on R&D).

94. Iain M. Cockburn, *The Changing Structure Of The Pharmaceutical Industry*, 23 HEALTH AFF., 10, 15 (2004).

to a boom in venture capital (“VC”) funds, which are the primary financiers of biotech companies. In 1979, the Department of Labor determined that pension funds could invest in VC funds; today pension funds are responsible for over 50% of the investment in VC funds.⁹⁵ Two years later, the Economic Recovery Tax Act of 1981 lowered the individual capital gains tax rate from 42% to 20%, incentivizing individual investment in VC funds.⁹⁶ As a result of these changes, VC funds more than doubled in the 3 years between 1979 and 1982.⁹⁷ Third, in 1980, issuance of the Cohen-Boyer patents covering recombinant DNA cloning opened the door for the patentability of discoveries in molecular biology.⁹⁸ Because early biotech companies generally had scientific ideas rather than tangible products, patents covering their discoveries were critical to instill confidence in investors that a proprietary concept could be commercialized before it was appropriated by someone else or developed elsewhere. Finally, the Bayh-Dole Act of 1980, for the first time, enabled non-government entities to patent discoveries emerging from federally-funded research.⁹⁹ These new patent rights encouraged biotech companies to collaborate with federally-funded research programs in government or academia and to invest the necessary time and money to develop and commercialize products.¹⁰⁰

More recently, new technologies have lowered some of the costs of early stage drug discovery. Computer-assisted drug design uses computer algorithms to identify the most promising molecules for new drugs, enabling much of the trial-and-error of early drug design to take place on computers instead of in the lab.¹⁰¹ Similarly, innovation in genome-sequencing technologies has greatly reduced the cost of sequencing DNA to identify genetic mutations that can lead to new drugs.¹⁰² These and other novel technologies enable early-stage drug

95. Douglas P. Lee & Mark D. Dibner, *The Rise of Venture Capital and Biotechnology in the US and Europe*, 23 NATURE BIOTECHNOLOGY 672, 673 (2005).

96. *Id.*

97. *Id.*

98. See Sally Smith Hughes, *Making Dollars Out of DNA*, 92 ISIS 541, 572 (2001) (describing how “[t]he encouragement and reassurance that the Cohen-Boyer patent and, to a lesser extent, other early patents in biotechnology contributed was significant in the formative stage of a commercial field in which proprietary rights to scientific processes and products were central and critical.”).

99. See 35 U.S.C. § 202(a)(1980) (“Each nonprofit organization or small business firm may, within a reasonable time after disclosure as required by paragraph (c)(1) of this section, elect to retain title to any subject invention.”).

100. Wendy H. Schacht, *The Bayh-Dole Act: Selected Issues in Patent Policy and The Commercialization of Technology*, CONG. RES. SERV., 8–9 (2012) (referencing studies that attribute to the Bayh-Dole Act increased collaboration between biotech companies and government entities and commercialization of federally funded research).

101. Petra Schneider & Gisbert Schneider, *De Novo Design at the Edge of Chaos*, 59 J. MED. CHEMISTRY 4077, 4079 (2016).

102. See Julie Steenhuysen, *How DNA Sequencing is Transforming the Hunt for New Drugs*, REUTERS (May 13, 2015), <http://www.reuters.com/article/us-health-precisionmedicine-insight-idUSKBN0NY0AX20150513>

design to occur at much lower cost, eliminating the advantage that large, resource-rich companies had over smaller biotechs at the preliminary stages of drug discovery.¹⁰³

Since the 1980s, the biotech industry has evolved to play a critical role in the pharmaceutical industry. The worldwide sales of biotech drugs have reached nearly \$300 billion, accounting for over 20 percent of worldwide drug sales.¹⁰⁴ Venture capital investment has risen correspondingly to fund the biotech industry. Whereas annual VC funding in the biotech sector rarely exceeded \$1 billion in the 1980s and early 1990s, VC funding increased by 842% between 1991 and 2001.¹⁰⁵ Between 2004 and 2008, VC firms invested \$21.5 billion in biotech drug R&D.¹⁰⁶ VC funding hit an all-time high in 2015,¹⁰⁷ with over \$7.5 billion raised for biotech companies in the pharmaceutical industry.¹⁰⁸

At the same time that the biotech industry boomed, traditional pharmaceutical companies have experienced a decrease in their internal R&D productivity. Money spent on internal R&D at large pharmaceutical companies is not producing the same returns it once did. Both the number of new patents

(providing that Regeneron Pharmaceuticals executives indicated that “they have used data from the first 35,000 volunteers to confirm the promise of 250 genes on a list of targets for drugs aimed at common medical conditions, including high levels of cholesterol and triglycerides.”).

103. *See generally*, Peter Gwynne & Gary Heebner, *Drug Discovery and Biotechnology Trends: Recent Developments in Drug Discovery: Improvements in Efficiency*, AM. ASS’N ADVANCEMENT SCI., (2017) http://www.sciencemag.org/site/products/ddbt_0207_Final.html (generally discussing newer technologies, such as high throughput screening systems, rational drug design, combinatorial chemistry, searchable chemical databases, and use of electronic laboratory notebooks that may help to reduce drug design costs in the biotech market).

104. DELOITTE, 2016 GLOBAL LIFE SCIENCES OUTLOOK, 3 (2015), <https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2016-life-sciences-outlook.pdf>.

105. LENA ANDREWS & JERRY PAYTAS, *BIORISING: VENTURE FIRMS REDISCOVER BIOTECH 1*, (Carnegie Mellon University)(2002).

106. Sy Mukherjee, *How VC Funding for Biotech has Fundamentally Changed—and What it Means for the Industry*, BIOPHARMA DIVE (June 3, 2015), <http://www.biopharmadive.com/news/how-vc-funding-for-biotech-has-fundamentally-changedand-what-it-means-for/399988/>

107. PRICEWATERHOUSECOOPER, *LIFE SCIENCES INVESTMENTS DEPART FROM YEAR-LONG HIGH*, 4 (2016), <https://www.pwc.com/us/en/health-industries/publications/assets/pwc-life-sciences-venture-funding-trends-2015-q4.pdf>.

108. *See* PRICEWATERHOUSECOOPER, *BIOTECH HITS RECORD FIRST QUARTER HIGH*, 2 (2015), <http://www.pwc.com/us/en/health-industries/publications/assets/pwc-biotech-trending-high-q1-2015.pdf> (VC investment for the biotech life sciences sector was \$1.7 billion in the first quarter of 2015); *see also*, PRICEWATERHOUSECOOPER, *LIFE SCIENCES FUNDING REACHES RECORD HIGH*, 2 (2015), <https://www.pwc.com/us/en/health-industries/publications/assets/pwc-moneytree-life-sciences-funding-reaches-q2-2015.pdf> (\$2.3 billion in the second quarter); *see also*, PRICEWATERHOUSECOOPER, *BIOTECH HOLDS STRONG AMID RECORD HIGH INVESTMENTS 2* (2015), <http://pwchealth.com/cgi-local/hregister.cgi/reg/pwc-life-sciences-money-tree-q3-2015.pdf> (\$2.1 billion in the third quarter); *see also*, PRICEWATERHOUSECOOPER, *LIFE SCIENCES INVESTMENTS DEPART FROM YEAR-LONG HIGH*, 2 (2016), <https://www.pwc.com/us/en/health-industries/publications/assets/pwc-life-sciences-venture-funding-trends-2015-q4.pdf> (\$1.5 billion in the fourth quarter).

per R&D dollar spent¹⁰⁹ and the revenue from new drugs per R&D dollar spent¹¹⁰ have declined steadily over the last decade as a result of a general increase in R&D spending paired with a leveling off of FDA approvals and a decrease in new drug sales. R&D spending has increased by approximately 145% since the early 2000s, from an estimated \$1.04 billion to \$2.6 billion to develop and bring each new drug to market.¹¹¹

The number of regulatory requirements imposed by the FDA has increased by 15 percent since the early 2000s.¹¹² The average number of patients required for clinical trials have increased,¹¹³ the costs of recruiting patients has increased, the clinical trial period has lengthened, and the number and complexity of clinical tests used in clinical trials have increased.¹¹⁴ The more stringent requirements, along with the more complex science associated with specialized medications, have significantly increased the costs of drug development and FDA approval.

Meanwhile, the returns from R&D have not increased to offset the increasing R&D costs. Although drug approval rates vary year-by-year, there has been no consistent increase in FDA approvals in recent decades.¹¹⁵ Moreover,

109. See Jack W. Scannel ET AL., *Diagnosing the Decline in Pharmaceutical R&D Efficiency*, 11 NAT. REV. DRUG DISCOVERY, 191, 192 (Mar. 2012) (demonstrating how the number of new drugs approved by the FDA per billion US dollars spent on research and development has halved roughly every 9 years).

110. See *Measuring the Return From Pharmaceutical Innovation: Balancing the R&D Equation*, DELOITTE (2016), <https://www2.deloitte.com/uk/en/pages/life-sciences-and-healthcare/articles/measuring-return-from-pharmaceutical-innovation.html> [hereinafter DELOITTE, *Pharmaceutical Innovation*], (demonstrating how returns from R&D continues to drop, with a projected drop of 3.7% in 2015)

111. See Joseph A. DiMasi ET AL., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 28 (2016) (demonstrating that “The base result is total cost per approved new compound for the DiMasi et al. (2003) study in year 2013 dollars (\$1044 million). The current study full cost estimate is 145% higher than the base result.”); see also Joseph A. DiMasi ET AL., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166 (2003) (providing that “[o]ur full cost estimate is the sum of our preclinical and clinical period cost estimates. Our base case out-of-pocket cost per approved new drug is US\$ 403 million, while our fully capitalized total cost estimate is US\$ 802 million.”)

112. Alexander Gaffney, *It's Not Just You: FDA Regulatory Requirements Really Are Increasing*, RAPS (Oct. 30 2014), <http://www.raps.org/Regulatory-Focus/News/2014/10/30/20656/Its-Not-Just-You-FDA-Regulatory-Requirements-Really-Are-Increasing/>

113. Grabowski, *supra* note 6, at 169.

114. *Id.*; See generally Kenneth A. ET. AL, *Variability in Protocol Design Complexity by Phase and Therapeutic Area*, 45 DRUG INFORM J., 413 (Jan. 2011) (discussing how the authors of 2008 study had found that “higher levels of protocol complexity were associated with longer clinical trial cycle times, higher levels of work effort to administer protocol procedures, and lower study volunteer randomization and enrollment rates.”).

115. See PHRMA, ANNUAL MEMBERSHIP SURVEY (2015), http://www.phrma.org/sites/default/files/pdf/2015-phrma_profile_membership_results.pdf (demonstrating how Industry R&D spending is shown in 2014 dollars and is based on members of the PhRMA trade association.); see also *Summary of NDA Approvals & Receipts, 1938 to the Present* (last updated Jan. 18, 2013), <https://www.fda.gov/aboutfda/whatwedo/history/productregulation/summaryofndaapprovalsreceipts1938tothepresent/default.htm> (demonstrating how New Drug Approvals show the approvals of new molecular

revenues from new drug sales have steadily declined;¹¹⁶ the average lifetime revenue for new drugs is lower now than at any point in the last 25 years.¹¹⁷ Thus, stagnating or falling returns combined with increasing R&D costs have led to a steady decline in internal R&D productivity.

B. The Relative Strengths of Biotech and Traditional Pharmaceutical Companies

Biotech companies generally differ from traditional pharmaceutical companies in a few critical areas that give these companies a comparative advantage in early-stage drug development. First, operating at a smaller size gives biotech companies important flexibility. Smaller companies generally have a less bureaucratic organization structure that allows for nimbler decision-making.¹¹⁸ With only a small group of key decision-makers, smaller companies can stay sharply focused on the company's strategic goals and make quick decisions to fund promising projects or kill unsuccessful projects at an early stage.¹¹⁹ In contrast, in larger companies with highly bureaucratic structures and multiple divisions, decision-making takes substantially longer and the optimal decision may sometimes succumb to office politics and competing conflicts of interest.¹²⁰

Second, biotech companies tend to have more geographic and personal links to nonprofit research institutions, such as research institutes and universities. In these institutions, academic scientists research questions and concepts in basic biomedical science without concern for the commercialization of any discoveries they make.¹²¹ In fact, the first biotech companies emerged as a result of revolutionary breakthroughs in basic science that took place in

entities, including both chemicals and biologics. Data on new drug approvals from 1980-2011); *see also* FDA, NOVEL DRUGS 2015 SUMMARY 5 (Jan. 2016), <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM481709.pdf> (finding that there has been very little consistent growth in the past decade).

116. DELOITTE, *Pharmaceutical Innovation*, *supra* note 110.

117. PHRMA, BIOPHARMACEUTICALS IN PERSP., *supra* note 33, at 44.

118. Grabowski, *supra* note 6, at 165.

119. *Pharmaceutical Innovation*, *supra* note 107; *see generally* Michael Mazzeo ET AL., *What Small Businesses Do Better Than Corporate America*, FORTUNE (Jun. 10, 2014) <http://fortune.com/2014/06/10/what-small-businesses-do-better-than-corporate-america/> (comparing the efficiencies of small businesses to their large corporate counterparts).

120. *Pharmaceutical Innovation*, *supra* note 107 (illuminating how aligning “end-to-end decision making across the organization” and striking “the right balance of staff and resource” increases R&D productivity and commercial success); *see also* Mazzeo, *supra* note 116 (explaining that smaller companies can exploit the “bureaucracy, corporate politics, and internal rivalries” that are present in big firms).

121. *See* Cockburn, *supra* note 94 at 15 (2004) (noting that “establishing priority and reputation drove early and extensive publication of results, and social norms (and requirements of granting agencies) promoted routine sharing of research materials” rather than commercialization).

universities in the 1970s.¹²² Many biotech companies continue to have academic scientists as their founders or chief scientific officers and are located near universities to encourage collaboration with researchers that remain in academia.¹²³ As the pace of discovery in basic biomedical science has accelerated with the mapping of the human genome and advances in bioinformatics, close contact between biotech companies and academic science has remained critical to the drug development process.¹²⁴

Third, in contrast to traditional pharmaceutical companies that generally finance their R&D spending from current revenues, biotech companies are typically funded by venture capital and private equity investments. In 2015, venture capitalists invested almost \$7 billion in biotech deals¹²⁵ and, with the exception of a few cyclical declines during economic downturns; VC investment in biotech has steadily increased since the early 1990s.¹²⁶ Venture capital funding enables biotech companies to take more risk on drug development projects than traditional pharmaceutical companies that are generally risking their own resources. In addition, the pressure of external funding with strict oversight by outside investment managers, pressure to meet timelines for each stage of development, and staged funding based on achieved milestones gives biotech companies a limited timeframe to demonstrate the value of projects, contributing to the culture of nimble decision-making; promising projects are accelerated while lagging projects are terminated quickly.¹²⁷

Finally, biotech's keen focus on strategic objectives, culture of creativity and innovation, and greater risk tolerance attracts the best scientists, many of whom leave traditional pharmaceutical companies for smaller biotech companies.¹²⁸ In biotech, the scientists generally avoid the administrative burdens and red tape that plague large pharma companies that are the enemy of

122. *Id.* at 15.

123. Grabowski, *supra* note 6 at 165.

124. *Id.*

125. DAVID THOMAS & CHAD WESSEL, EMERGING THERAPEUTIC COMPANY INVESTMENT AND DEAL TRENDS: US VENTURE CAPITAL AND PUBLIC OFFERINGS, 2006-2015 CURRENT PIPELINE FOR EMERGING COMPANIES 3(2016).

126. Douglas Lee & Mark Dibner, *The Rise of Venture Capital and Biotechnology in the US and Europe*, 23 NATURE BIOTECHNOLOGY 672, 673 (2005).

127. DELOITTE CENTRE FOR HEALTH SOLUTIONS, BALANCING THE R&D EQUATION: MEASURING THE RETURN FROM PHARMACEUTICAL INNOVATION 30 (2016),

128. *See generally* Jennifer Alsever, *Big Pharma Innovation in Small Places*, FORTUNE (May 13, 2016), <http://fortune.com/2016/05/13/big-pharma-biotech-startups/> (reporting that more top executives are leaving large pharmaceutical companies for biotech startups); *See* Erika Check Hayden, *Young Scientists Ditch Postdocs for Biotech Start-ups*, NATURE (Nov. 1, 2016), <http://www.nature.com/news/young-scientists-ditch-postdocs-for-biotech-start-ups-1.20912#auth-1> (reporting that many young biomedical scientists are starting their own companies rather than taking a more traditional path); Jonathan Rockoff, *Big Pharma, Short on Blockbusters, Outsources the Science*, WALL STREET J. (Dec. 7, 2016), <http://www.wsj.com/articles/big-pharma-short-on-blockbusters-outsources-the-science-1481042583>.

innovation.¹²⁹ Instead, the scientists are involved on a daily basis with discovery and innovation, the reasons they originally entered the field. The greater risk tolerance of biotech companies allows scientists to pursue projects they might not be able to pursue in a more risk-averse pharmaceutical company. Moreover, smaller biotech companies often include stock options in compensation packages, giving scientists a big reward when projects prove successful.¹³⁰ As research scientists have steadily moved into biotech, the innovation has followed; biotech companies now account for approximately two-thirds of NMEs approved by the FDA¹³¹ and 70% of drugs currently in the pipeline.¹³²

Just as biotech companies have a comparative advantage in early-stage development, large pharmaceutical companies have advantages in the more advanced stages of development and in the production, marketing, and distribution of drugs. The large pharmaceutical companies' significant cash reserves allow them to provide funding for expensive clinical trials in the late stages of drug development.¹³³ These companies also generally have considerable experience in both large-scale clinical trial design and in coordination of various regulatory requirements.¹³⁴ They can provide the operational scale in manufacturing, existing distribution networks, and colossal sales forces necessary to achieve rapid uptake of new products.¹³⁵ And they have learned to maneuver through the red tape of the commercialization process, including regulations on drug promotion, patent exclusivity, payer negotiations, taxes, and much more.¹³⁶

The industry has responded to the relative strengths of biotech versus traditional pharma by fostering an innovation ecosystem where larger pharmaceutical companies increasingly look externally for R&D.¹³⁷

129. Tom Hughes, *Should I Stay or Should I Go? Big Pharma Execs taking the Biotech Plunge*, LIFE SCI. VC (Oct. 6, 2014), <https://lifescivc.com/2014/10/should-i-stay-or-should-i-go-big-pharma-execs-taking-the-biotech-plunge/>.

130. Mark Terry, *Biotech vs. Big Pharma: Which is the Better Place to Work?* BIOSPACE (Sept. 19, 2016), <http://www.biospace.com/News/biotech-vs-big-pharma-which-is-the-better-place-to/432908> (comparing and contrasting biotech companies and pharmaceutical companies and explaining that stock options are attractive aspects of biotech startups, but should be kept in perspective).

131. See Ulrich Geilinger et. al., *Trends in US New Drug Approvals*, (Feb. 2016), <http://www.hbmpartners.com/wAssets/docs/industry-reports/HBM-Report-Trends-in-US-New-Drug-Approvals-2006-2015.pdf> (indicating two thirds of NMEs approved by the FDA are now accounted for by biotechs, signaling a move by research scientists into biotech).

132. THOMAS & WESSEL, *supra* note 86, at 30.

133. Wendy Tsai & Stanford Erickson, *Early-Stage Biotech Companies: Strategies for Survival and Growth*, 3 BIOTECHNOLOGY HEALTHCARE, 49, 50–52 (2006).

134. Grabowski, *supra* note 6 at 173.

135. Tsai & Erickson, *supra* note 133, at 50–52.

136. Nicole Fisher & Scott Liebman, *Are M&A replacing R&D in Pharma*, FORBES (Apr. 22, 2015), <http://www.forbes.com/sites/nicolefisher/2015/04/22/are-ma-replacing-rd-in-pharma/#754cc4d6cb57>.

137. See Lisa LaMotta, *How Incubators are Accelerating Early Drug Development*, BIOPHARMA DIVE (Nov. 7, 2016), <http://www.biopharmadive.com/news/incubators-biotechs-early-drug->

Increasingly, innovation originates in biotech companies, where the culture, risk tolerance, and strategic goals encourage early-stage development. To complete the development process and commercialize their drugs, biotech companies regularly collaborate with large pharmaceutical companies that push drugs through the grueling late-stage clinical trials and regulatory hurdles of the FDA, organize their manufacturing and distribution capabilities to bring the drug to market, and mobilize their vast sales force to quickly achieve peak sales. By concentrating on their comparative advantages, both biotech and large pharma companies improve on their strengths without being hindered by their weaknesses.

Whereas in the 1970s and early 1980s, almost all drug discoveries took place inside traditional pharmaceutical companies,¹³⁸ today pharmaceutical companies increasingly look to collaborations with biotech companies and other external entities.¹³⁹ These collaborations often take the form of licensing deals, co-development alliances to share costs and risks, equity-based joint ventures, and mergers and acquisitions.¹⁴⁰ As a result, the share of internally-developed versus externally-developed drugs has changed dramatically as traditional pharmaceutical companies have shifted resources away from internal R&D expenditures and projects and towards external sources of innovation.¹⁴¹ Externally-sourced drugs now account for an incredible 74 percent of new drugs registered with the FDA for sale in the U.S.¹⁴² However, traditional pharmaceutical companies remain active in the innovation process through collaborations; 60-70 percent of large pharmaceutical companies' drug approvals are the result of licensing deals and mergers or acquisitions.¹⁴³ Moreover, for some large pharmaceutical companies that appreciate the role of alliances in

development/429614/. Recognizing biotech's advantage in early-stage innovation, large pharmaceutical companies have recently formed divisions aimed at replicating the biotech culture. Pharmaceutical giants such as Pfizer, Bayer, and Johnson & Johnson have funded "incubators" that give academic scientists and biotech entrepreneurs valuable space, equipment, resources, and connections to reproduce the biotech environment. In return, the pharmaceutical companies are given some level access to the early-stage innovation developed in the incubators. *Id.*

138. See Grabowski, *supra* note 6, at 165 (stating in the 1970s and early 1980s almost all drug discovery took place within traditional pharmaceutical companies).

139. See Serge Mignani ET AL., *Why and How Have Drug Discovery Strategies in Pharma Changed? What are the New Mindsets?*, 21 DRUG DISCOVERY TODAY 239, 242 (2016) (reporting that "half of all drugs are developed through collaborations").

140. *Id.*

141. John LaMattina, *There's Value in Studying Big Pharma Pipelines*, FORBES (Jan. 14, 2013, 8:41 AM) ("Pfizer has been out-licensing a number of early development compounds as it has slashed its R&D budget. As a result, its pipeline which contained 114 compounds in February, 2011 now has the aforementioned 78.").

142. QUINTILES IMS INSTITUTE, LIFETIME TRENDS, *supra* note, at 12.

143. MURRAY AITKEN & MICHAEL KLEINROCK, LIFETIME TRENDS IN BIOPHARMACEUTICAL INNOVATION: RECENT EVIDENCE AND IMPLICATIONS 1 (2017), https://www.statnews.com/wp-content/uploads/2017/01/Lifetime_Trends_in_Biopharmaceutical_Innovation.pdf.

expanding their innovation pipelines, this percentage is even higher. For example, in 2016, 92 percent of Allergan's top-25 drugs were externally sourced.¹⁴⁴

That pharmaceutical companies have turned to external sources for a significant share of their innovative products is no surprise given the strengths and weaknesses of biotech companies and traditional pharmaceutical companies. Indeed, research finds benefits to innovation when biotech firms and large pharma companies specialize based on their comparative advantages. Drug products developed in alliances have a higher probability of success in late-stage clinical trials relative to drugs developed by the originator firm,¹⁴⁵ regardless of whether the originator firm is small or large.¹⁴⁶ This is especially true when the licensing firm has more experience than the drug originator, as is generally the case with alliances between smaller biotech companies and larger pharmaceutical companies.¹⁴⁷ In fact, when measured from the original FDA application to final approval, externally-sourced drugs have almost double the success rate as internally-developed drugs.¹⁴⁸ Mergers too, as distinct from alliances, increase the success of drug products in clinical trials; projects initiated after a merger are much more likely to advance from each stage of development.¹⁴⁹

Moreover, alliances and mergers can have longer-term impacts on innovation. Evidence shows that R&D alliances help biotech firms establish a position within a network of firms, which in turn leads to increases in patents and sales revenue.¹⁵⁰ Further, when pharmaceutical companies acquire smaller biotech companies, the post-merger product pipelines generally improve, creating longer-term advances in innovation.¹⁵¹

144. ALLERGAN, OPEN SCIENCE TAKEAWAYS: INTERNAL ANALYSIS (2016).

145. Patricia M. Danzon ET AL., *Productivity in Pharmaceutical-biotechnology R&D: The Role of Experience and Alliances*, 24 J. HEALTH ECON. 317, 337–38 (Jan. 2005), <http://www.fep.up.pt/docentes/pcosme/Artigos/49-JHE.pdf>; See Sean Nicholson ET AL., *Biotech-pharmaceutical Alliances as a Signal of Asset and Firm Quality*, 78 J. BUS. 1433, 1434 (2005), https://faculty.wharton.upenn.edu/wp-content/uploads/2014/10/biotech-pharmaceutical-alliances_1.pdf (describing a number of strategies and the economics of joint ventures).

146. Danzon et al., *supra* note 145.

147. Danzon et al., *supra* note 9, at 321–38.

148. Bruce Booth, *Positive Impact of External Sourcing on R&D Productivity*, FORBES (Dec. 16, 2016, 7:18 AM), <http://www.forbes.com/sites/brucebooth/2016/12/16/positive-impact-of-external-sourcing-on-pharma-rd-productivity/amp/> (last visited Mar. 30, 2017).

149. Grabowski & Kyle, *supra* note 8, at 283.

150. Walter W. Powell et al., *Network Position and Firm Performance: Organizational Returns to Collaboration in the Biotechnology Industry*, in NETWORKS IN AND AROUND ORGANIZATIONS 1, 24–26 (Steven Andrews & David Knoke, eds., 1999), <https://web.stanford.edu/~woodydp/papers/Rso1.pdf>.

151. See Higgins & Rodriguez, *supra* note 9 at 352.

III. THE PROPER ANALYSIS OF CONSOLIDATION'S IMPACT ON INNOVATION

Despite concerns among some researchers and competition agencies that consolidation in the pharmaceutical industry reduces innovation, aggregate innovation has held strong notwithstanding dramatic increases in M&A activity. The years 2014 and 2015 generated both record numbers of new drug approvals and record pharmaceutical M&A.¹⁵² In fact, although M&A deals and new drug approvals vary slightly year-to-year, the general pattern has been increasing aggregate innovation alongside increasing consolidation.¹⁵³

Although trend data is not enough to prove a causal relationship between innovation and consolidation, when considered alongside the evolving innovation ecosystem, it suggests that M&A does not stifle drug innovation. Today, most drug innovation originates outside of traditional pharmaceutical companies, in biotech companies and smaller firms, where a culture of nimble decision-making and risk-taking facilitates discovery and innovation. In the later stages of the drug development process, the biotech companies routinely partner with large pharmaceutical companies to advance through late-stage clinical trials and produce, market, and distribute the drugs.¹⁵⁴ In this current ecosystem, biotech and pharmaceutical firms are able to specialize in what they do best, bringing expertise and efficiencies to the innovation process. The specialization has led to an environment in which approximately three-fourths of new drugs are externally-sourced.¹⁵⁵ Internal R&D is no longer the primary source, or even an important source, of drug innovation.

As a result, analyses that focus on mergers' impacts on internal R&D and innovation are largely missing the point. In the current innovation ecosystem, where little drug innovation originates internally, a merger's impact on internal R&D expenditures or development projects is oftentimes immaterial to aggregate drug innovation. Although concerns about the effect of consolidation on internal innovation were well-founded a few decades ago, and may still be relevant in certain situations, they are, for the most part, misplaced today.

Instead, researchers and enforcement agencies concerned with impacts on innovation should focus on whether consolidation enables firms to better support drug innovation in the current ecosystem. Many mergers are aimed at reducing

152. See U.S. FOOD & DRUG ADMIN., NOVEL DRUGS SUMMARY 2016 2, 3 (2017), <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM536693.pdf> (showing that in 2014, 41 drugs were approved, and in 2015, 45 drugs were approved); see also MERGERMARKET, PHARMA, MEDICAL, & BIOTECH TREND REPORT: Q1-Q4 2016 2 (2017), <http://www.mergermarket.com/pdf/MergermarketTrendReport.Q1Q42016.Pharma,Medical,Biotech.pdf> (showing that in 2014, there were 442 mergers worth \$260.9 billion, and in 2015, there were 506 mergers worth \$161.7 billion).

153. See MERGERMARKET, *supra* note 3, at 2.

154. See Mignani ET AL., *supra* note 139, at 242.

155. See AITKEN & KLEINROCK, *supra* note 89, at 1.

costs and increasing efficiencies in the consolidated firms.¹⁵⁶ If firms realize these gains, they should be in a better position to support external innovation. In the consolidated firms, increases in efficiency and streamlining of operations will free up money and resources to source external innovation. To improve their future revenue streams and market share, consolidated firms should use at least some of the extra resources to acquire external innovation. This increase in demand for externally-sourced innovation will, in turn, increase the prices paid for external assets. Indeed, mirroring the increase in demand for external innovation, both acquisition prices and payments to license R&D-stage assets from biotech and emerging companies have increased.¹⁵⁷ Increasing prices for R&D stage assets incentivize more early-stage innovation in small firms and biotech companies, increasing aggregate innovation in the process.

Thus, proper analyses of the impacts of consolidation on innovation must take into account the current innovation ecosystem in which most innovation originates externally. Concerns about harms to innovation could be relevant in specific mergers or acquisitions if the consolidating firms are the primary innovators in the area, the firm innovates internally, and there are essentially no sources of external innovation. However, such scenarios are increasingly rare in the current ecosystem. As long as there is sufficient market competition so that firms must innovate to ensure their future profitability and market share, consolidation will often allow firms to devote more resources to externally-sourced innovation. The increased demand for externally-sourced innovation will, in turn, spur incentives to innovate in biotech and small companies. Therefore, merger analyses should be less concerned with the impact consolidation will have on internal innovation, and more focused on whether consolidation will increase demand for externally-sourced innovation and, ultimately, increase aggregate drug innovation.

CONCLUSION

The pharmaceutical industry has undergone a significant transformation in recent decades. The intensifying competition from generics, expanding power of pharmaceutical payers, increasing costs of drug development, and growing risks of commercial failure have dramatically changed the industry's economic environment and strained the finances of traditional pharmaceutical firms. Many firms have responded by consolidating to either reduce costs or create new sources of revenue.

As pharmaceutical M&A has soared, so too has concern over the impacts of consolidation on the industry. While most of the scrutiny has focused on harms

156. See Grabowski, *supra* note 6 at 173 (noting that pharmaceutical industry mergers boosted short-term earnings).

157. See DAVID THOMAS & CHAD WESSEL, *supra* note 88 at 30.

to competition, researchers and agencies have also raised less-traditional concerns about harms to innovation in the newly-merged firms. However, these innovation concerns are, for the most part, based on an outdated understanding of the drug innovation ecosystem. Whereas a few decades ago almost all drug discovery took place inside traditional pharmaceutical companies, today most drug innovation is externally-sourced from biotech companies and smaller firms. Internal R&D is no longer the primary source, or even an important source, of drug innovation in large pharmaceutical companies. As a result, merger analyses that focus on the impact of pharmaceutical consolidation on internal innovation are incomplete because they fail to recognize that consolidation can increase demand for externally-sourced innovation and, ultimately, strengthen aggregate drug innovation.

Pharmaceutical industry analysts expect the already heightened pace of M&A activity to pick up under the Trump administration, as soaring stock prices and favorable tax reforms boost deal-making.¹⁵⁸ Policy makers must understand the role of consolidation in the current innovation ecosystem and evaluate mergers for their likely impacts on aggregate drug innovation.

158. Carl O'Donnell, *Trump Presidency Could Prove a Salve for Pharma Merger Deals*, REUTERS (Nov. 11, 2016), <http://www.reuters.com/article/us-usa-election-biotech-m-a-idUSKBN1360DC>.