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The Uneasy Case for Patent Law

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THE UNEASY CASE FOR PATENT LAW

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A central tenet of patent law scholarship holds that if any scientific field truly needs patents to stimulate progress, it is pharmaceuticals. Patents are thought to be critical in encouraging pharmaceutical companies to develop and commercialize new therapies, due to the high costs of researching diseases, developing treatments, and bringing drugs through the complex, expensive approval process. Scholars and policymakers often point to patent law's apparent success in the pharmaceutical industry to justify broader calls for more expansive patent rights.

This Article challenges this conventional wisdom about the centrality of patents to drug development by presenting a case study of the role of patents in the emerging field of microbiome research. Scientists have recently begun to appreciate the important role played by the human microbiome, the community of microbes that lives within each of our bodies, in preventing and treating disease. The microbiome has been linked to autoimmune disorders, mental health conditions, and a range of conditions affecting our intestinal systems. Put simply, research involving the microbiome has the potential to change the future of medicine.

There's just one problem: the microbiome can't meaningfully be patented. Several doctrines within patent law will make it extremely difficult for companies to obtain and enforce patents like the ones that are so readily available in most areas of medicine. Drawing on patent doctrine, patent searches, and interviews with scientists and lawyers, this Article demonstrates that companies are developing microbiome-based therapies largely in the absence of patent protection. Instead, the companies are relying on other innovation incentives to fill the gap.

The microbiome's unpatentability presents an opportunity to evaluate whether patents are truly necessary for the development of new drugs. Congress, the NIH, and the FDA have implemented many innovation incentives throughout the development process, and we should not be astonished that

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removing a single such incentive, patent law, does not disrupt the entire system. Perhaps scholars should reconsider, if only selectively, our focus on patents as an irreplaceable driver of pharmaceutical innovation.

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Introduction

The pharmaceutical industry has long been held out as the paradigm example of the ability of patents to promote innovation. The process of developing new drugs is long, expensive, and risky, and scholars and policymakers argue that without the availability of patent protection, pharmaceutical companies would not make the investments needed to bring new drugs to market.[1] If anything, the prevailing scholarly debate is over whether patent

1. *See, e.g.*, Fed. Trade Comm'n, To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy ch. 3, at 14 (2003); Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 Va. L. Rev. 1575, 1616–17 (2003).

protection for pharmaceuticals is too short, rather than too long,[2] as drugs have still not been developed for many diseases that are devastating to our healthcare system.[3]

An emerging new field of drug discovery now provides a test of the veracity of this conventional wisdom. Over the past decade, there has been an explosion of scientific interest in the microbiome: the community of microbes that lives within each of our bodies and exists in a symbiotic relationship with us.[4] Scientists and pharmaceutical companies have become interested in using the microbiome to fight and even prevent disease. If the conventional wisdom is to be believed, these companies must be applying for and utilizing robust patent portfolios as they traverse the FDA approval process. But they are not.

At one level, this Article presents a case study of the role of patent law in the emerging field of microbiome research. The dozens of companies already operating in this space are largely eschewing traditional patent protection, both because doctrinal barriers exist to obtaining patents and because practical barriers exist to their enforcement. Instead, these companies are relying on a range of other innovation incentives to protect their investments. Some of these incentives have been specifically designed to operate in the pharmaceutical space, such as FDA exclusivity periods, while others are more general, such as trade secrets. The picture is one of a growing, thriving sector of the biotechnology industry, operating largely without a tool that has long been viewed as an essential incentive mechanism.

Yet at another level, this Article challenges the conventional wisdom about the centrality of patents to the drug-development process. If patents are not necessary to encourage companies to move into this area of pharmaceutical investment, are they truly necessary to the industry as a whole? Over the last several decades, fears about insufficient investment in pharmaceuticals have led Congress,[5] the NIH,[6] and the FDA[7] to develop and implement a

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2. *See, e.g.*, Eric Budish et al., *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 Am. Econ. Rev. 2044, 2045 (2015); Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. Rev. 672, 751–53 (2014).

3. Rachel E. Sachs, *Prizing Insurance: Prescription Drug Insurance as Innovation Incentive*, 30 Harv. J.L. & Tech. 153, 155–56 (2016).

4. Ed Yong, I Contain Multitudes 2–3, 5 (2016).

5. 42 U.S.C. § 262(k)(7)(A) (2012) (Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, § 7002, 124 Stat. 804, 807, conferring twelve years of data exclusivity); 21st Century Cures Act, H.R. 34, 114th Cong. § 2002 (2016) (enacted).

6. *Federal Prize Competition Seeks Innovative Ideas to Combat Antimicrobial Resistance*, Nat'l Insts. Health (Sept. 8, 2016), https://www.nih.gov/news-events/news-releases/federal-prize-competition-seeks-innovative-ideas-combat-antimicrobial-resistance [https://perma.cc/HNN5-TPRB]; *About the BRAIN Initiative: The Initiative Kicks Off*, White House (2016), https://obamawhitehouse.archives.gov/node/300741 [https://perma.cc/5HYU-CSR9].

broad range of innovation incentives operating on different actors at different points in the development process. Many of these incentives have duplicated at least some of the functions of patent law itself.[8] Perhaps we should not be astonished that removing a single one of these incentives, patent law, does not disrupt the entire system.

Part I of this Article considers the role played by patent law in the pharmaceutical industry. It begins by explaining the ways in which patents are thought to operate to promote investment in pharmaceuticals before situating them within a broader context of innovation incentives operating in this area. Part II first provides a brief orientation to the emerging field of microbiome research, explaining how scientists have linked the microbiome to human disease and considering the many ways in which companies have begun using the microbiome to develop medical treatments. Part II goes on to consider the ways in which the innovation incentives described in Part I might play out in the microbiome context.

Part III then introduces a key problem: the microbiome can't be protected by patents in the way that other pharmaceutical technologies can. First, there are multiple doctrinal barriers preventing these companies from obtaining product patents covering their therapies. The patentable subject matter, written description, and enablement requirements will pose obstacles here. Second, even where companies have obtained less valuable method claims, they will confront enforcement difficulties that do not arise in the context of other pharmaceuticals. Difficulties surmounting the divided infringement bar and practical concerns involving detection and enforcement will create problems. Importantly, these concerns are not merely doctrinal ones drawn from case law—they are supported by searches of granted patents.

Part IV goes on to present the results of a series of structured interviews I held with people in the field: scientists from both industry and academia, the IP attorneys advising them, and technology-transfer officers at universities. In short, companies are moving forward and developing microbiome-based therapies with thin, if any, patent protection. Instead of relying primarily on patent protection, companies are increasingly relying on other innovation incentives to fill the gap left behind. For example, companies are relying on trade secrecy to protect their manufacturing processes and donor information, and they are looking forward to the prospect of twelve years of biologic-drug exclusivity after FDA approval. Many deals have been executed between universities and small companies or between small companies and large companies without patents to facilitate them.

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7. 21 U.S.C. § 360n (2012) (establishing a priority review voucher system for neglected tropical diseases); The Ctr. for Health Policy at Brookings, Breakthrough Therapy Designation 3 (2015).

8. *See, e.g.*, Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 Mich. Telecomm. & Tech. L. Rev. 419, 423 (2012).

Part V revisits the conventional wisdom around pharmaceutical patents in light of this case study. The unpatentability of the microbiome presents an opportunity to evaluate whether patents are truly necessary for the development and commercialization of new treatments, not only in the microbiome context but also more generally. To the extent that the rest of the innovation ecosystem that policymakers have built up around pharmaceuticals is largely sufficient to entice drugs through the development process, scholars should reconsider our academic focus on patents as an irreplaceable driver of innovation incentives.

I. The Role of Patent Law in the Pharmaceutical Industry

Patent scholars, industry representatives, and policymakers often debate the role our patent system plays in different technological sectors. However, there is general agreement on one thing: if there is any field where patent protection is critical, it is the pharmaceutical field. Due to the high costs of researching diseases, developing treatments, and traversing the FDA approval process, patents are thought to be necessary to encourage pharmaceutical companies to develop and commercialize new therapies. In this Part, I will first unpack this conventional wisdom, explaining why patents may be of special importance in this field relative to other technological areas. I will then situate patents within the broader innovation ecosystem surrounding pharmaceuticals, noting their similarities and differences to other special incentives created for these technologies.

A. *Patents' Importance to the Pharmaceutical Industry*

The patent statute is almost entirely one-size-fits-all,[9] in the sense that inventions from vastly different technological areas must meet the same legal requirements to be patented and receive the same legal protections when those patents are granted.[10] On its face, the statute is technology neutral.[11] It is not obvious that this should be so, depending on our reasons for adopting and tailoring the patent scheme. Is a twenty-year fixed patent term equally needed for software, where the typical product lifecycle is just a few years,

9. The exceptions here, like the Semiconductor Chip Protection Act of 1984, prove the rule. Pub. L. No. 98-620, 98 Stat. 3347 (codified at 17 U.S.C. §§ 901–14 (2012)).

10. Burk & Lemley, *supra* note 1, at 1577. For a more general treatment of this issue, see Michael W. Carroll, *One for All: The Problem of Uniformity Cost in Intellectual Property Law*, 55 Am. U. L. Rev. 845 (2006), and Michael W. Carroll, *One Size Does Not Fit All: A Framework for Tailoring Intellectual Property Rights*, 70 Ohio St. L.J. 1361 (2009).

11. In practice, the courts have interpreted these technology-neutral laws in ways that have different ramifications for different industries. Burk & Lemley, *supra* note 1, at 1577. However, the facially neutral patent statute still presents a stark contrast to the technology-specific Copyright Act. *See, e.g.*, *id.* at 1638; Jessica Litman, *Copyright Legislation and Technological Change*, 68 Or. L. Rev. 275, 277, 333–34 (1989).

and for pharmaceuticals, where the typical product lifecycle is far longer?[12] Should the same procedural rules apply to litigation in the software or business-method context, where patent trolls are much more prevalent,[13] as to litigation involving chemical or pharmaceutical patents?

Scholars can more easily reach agreement on these questions if we can agree on the underlying purposes of patent law,[14] because we can then consider whether particular doctrinal choices accord well with those purposes. To be sure, there may be barriers preventing scholarly consensus from translating into doctrinal change. Political considerations may create difficulties for domestic reform.[15] The requirement that patent terms last twenty years irrespective of technological field is not merely a creation of United States law but is instead enshrined in an international treaty,[16] which is unlikely to change anytime soon. But there is still a great deal of flexibility for existing law to be tailored by technological field.

The purposes of patent law are most succinctly stated in the Constitution itself: patents serve to "promote the Progress of Science and useful Arts."[17] Most scholars and judges therefore take a largely consequentialist view of patents.[18] On this view, patents primarily function to encourage inventors to develop inventions and to encourage companies to commercialize those inventions.[19] Patents may also serve a valuable disclosure function, dis-

12. Burk & Lemley, *supra* note 1, at 1622; *see also* Julie E. Cohen & Mark A. Lemley, *Patent Scope and Innovation in the Software Industry*, 89 CALIF. L. REV. 1, 39, 46 (2001).

13. *But see* Robin Feldman & W. Nicholson Price II, *Patent Trolling: Why Bio & Pharmaceuticals Are at Risk*, 17 STAN. TECH. L. REV. 773, 775–77 (2014).

14. This is not required. Scholars taking different views of the purposes of the patent system may nonetheless find agreement on the policy outcomes encouraged by disparate theories. There is room for overlapping consensus here. However, it may be easier to reach agreement when all parties agree on the nature of the problem to be solved. *See, e.g.*, Cass R. Sunstein, Commentary, *Incompletely Theorized Agreements*, 108 HARV. L. REV. 1733, 1735–37 (1995).

15. Rachel Sachs, *The New Model of Interest Group Representation in Patent Law*, 16 YALE J.L. & TECH. 344, 392 (2014).

16. TRIPS: Agreement on Trade-Related Aspects of Intellectual Property Rights art. 33, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994), https://www.wto.org/english/docs_e/legal_e/27-trips_04c_e.htm#5 [https://perma.cc/7UJZ-6VCL] ("The term of protection available shall not end before the expiration of a period of twenty years counted from the filing date."); DAN L. BURK & MARK A. LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT 97 (2009).

17. U.S. CONST. art. I, § 8, cl. 8.

18. Mark A. Lemley, *Ex Ante Versus Ex Post Justifications for Intellectual Property*, 71 U. CHI. L. REV. 129, 129–30 (2004). Not all scholars share this view. *See, e.g.*, ROBERT P. MERGES, JUSTIFYING INTELLECTUAL PROPERTY 2–4 (2011); Adam D. Moore, *Intellectual Property, Innovation, and Social Progress: The Case Against Incentive Based Arguments*, 26 HAMLINE L. REV. 601, 630 (2003).

19. *See, e.g.*, Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 YALE L.J. 1900, 1904 (2013). In some technological fields, these two in-

closing information about the invention in question to the public as the price of obtaining the right to exclude.[20] Certainly, there are problems with and gaps in these incentives. Patents' incentive and disclosure functions may break down in different circumstances.[21] But in theory, patents serve as a powerful motivator enabling private inventors to recoup their investments in the development of new technologies by excluding others from copying those technologies for a period of time.

Yet the benefits of the patent system come with important costs. Chiefly, the inventor's right to exclude enables them to charge higher prices, forcing at least some consumers out of the relevant market and decreasing access to the technology in question.[22] We might also worry about tradeoffs between different kinds of innovation. Scholars have expressed concern that patents on one generation of technologies or research tools may impede follow-on research,[23] or that patents may make certain kinds of research more financially attractive than others in ways that do not align with the social value of the inventions to be pursued.[24] Given these concerns, if patents are not needed to call a new invention into being, scholars should be concerned about granting these patents, because in that case the public would not be receiving the benefits of patents in the form of new technologies but would still suffer the social welfare harms. These tradeoffs are complex, but for my purposes it is sufficient that the prevailing scholarly perspective is one of patents as tools to promote innovation.

On this view of the patent system, it becomes clear that patents may succeed in driving innovation more or less strongly in different industries. Consider patents on business methods or software claims. Leading scholars have argued persuasively that lengthy patents are not necessary to encourage innovation in these areas, given the low costs and short time to market required in developing the technologies, first-mover advantages, and the short

centives—invention and commercialization—may largely collapse into each other. However, in other fields (including pharmaceuticals, as I explain in Section I.B *infra*), the cost of developing and commercializing a drug is much higher than the cost of identifying a candidate compound in the first instance.

20. Clark D. Asay, *The Informational Value of Patents*, 31 Berkeley Tech. L.J. 259, 269–70 (2016).

21. Peter S. Menell & Michael J. Meurer, *Notice Failure and Notice Externalities*, 5 J. Legal Analysis 1, 32–34 (2013) (detailing ways in which patent disclosures are often inadequate to provide notice of what is protected); Ted Sichelman, *Commercializing Patents*, 62 Stan. L. Rev. 341, 343–44 (2010) (arguing that patent law serves the development and commercialization function poorly).

22. *See* Suzanne Scotchmer, Innovation and Incentives 58 (2004); Rochelle Cooper Dreyfuss, Essay, *Are Business Method Patents Bad for Business?*, 16 Santa Clara Computer & High Tech. L.J. 263, 275 (2000).

23. Burk & Lemley, *supra* note 1, at 1618, 1623; Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 Science 698 (1998).

24. Kapczynski & Syed, *supra* note 19, at 1907.

product life cycles involved.[25] Several members of the judiciary share these views,[26] constraining the types of patents that may be granted in these areas but not categorically barring their availability.[27] Perhaps most importantly, when asked about the importance of patents to innovation in their fields, software entrepreneurs generally report that patents provide little or no incentive to invent.[28] And given the high costs imposed on these industries by vexatious litigation, including limits on innovative downstream activity,[29] it is not obvious that patents are on balance beneficial in these fields.

The story in the pharmaceutical industry could not be more different. Pharmaceuticals are among the most costly products to develop and bring to market, with most estimates putting the cost of developing a new drug at well over a billion dollars.[30] The process is also quite lengthy, on average taking twelve to sixteen years from inception until FDA approval.[31] Drug development is risky as well. Most drugs fail after companies have invested hundreds of millions of dollars developing them.[32] But once developed, most drugs are simple to imitate. The time and cost required to develop a generic small-molecule drug is far lower than the time required to bring an innovator drug to market; the generic can take less than two years' time and about $2 million.[33]

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25. Burk & Lemley, *supra* note 1, at 1618, 1622–23; Dreyfuss, *supra* note 22, at 275.

26. *See, e.g.*, Alice Corp. v. CLS Bank Int'l, 134 S. Ct. 2347, 2360 (2014) (Sotomayor, J., concurring); Bilski v. Kappos, 561 U.S. 593, 613–14 (2010) (Stevens, J., concurring in the judgment); *In re* Bilski, 545 F.3d 943, 1006 (Fed. Cir. 2008) (en banc) (Mayer, J., dissenting).

27. See *infra* Section I.B for a more detailed explanation of this precedent.

28. Stuart J.H. Graham et al., *High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey*, 24 Berkeley Tech. L.J. 1255, 1286 (2009).

29. That is to say, it is not just expensive to defend against these suits. They may pause research projects, or shut them down entirely. *See, e.g.*, James Bessen, *The Evidence Is In: Patent Trolls Do Hurt Innovation*, Harv. Bus. Rev. (Nov. 2014), https://hbr.org/2014/07/the-evidence-is-in-patent-trolls-do-hurt-innovation (on file with the *Michigan Law Review*).

30. The cost of pharmaceutical development is a topic of intense debate. *Compare* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 20 (2016) (estimating pre-approval costs to be $2.558 billion), *with* Donald W. Light & Rebecca Warburton, *Demythologizing the High Costs of Pharmaceutical Research*, 6 BioSocieties 34, 46–47 (2011) (estimating the cost at $43.4 million). However, there is broad agreement that pharmaceuticals are highly expensive goods to develop. *See* Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 San Diego L. Rev. 419, 426, 448–57 (2014).

31. Roin, *supra* note 2, at 719.

32. Michael Hay et al., *Clinical Development Success Rates for Investigational Drugs*, 32 Nature Biotechnology 40 (2014).

33. *See* Thomas Sullivan, *FDA Under Pressure to Speed Up Generic Approvals*, Pol'y & Med., https://www.policymed.com/2017/04/fda-under-pressure-to-speed-up-generic-approvals.html [https://perma.cc/Q2FQ-QRVP] (last updated May 4, 2018). Although generic drug approval times can be longer, particularly if the FDA must send the application back for more information, the mean approval time for all generic drugs has dropped to 35.3 months in the third quarter of 2018. *Activities Report of the Generic Drugs (FY 2018) – GDUFA II Quar-*

Scholars point to these high fixed costs, the risk and time required, and the ease of imitation in concluding that "[s]trong patent rights are necessary to encourage drug companies to expend large sums of money on research years before the product can be released to the market."[34] Even the Federal Trade Commission has referred to innovation in the pharmaceutical industry as "showcas[ing] the patent system's benefits."[35] Industry agrees. Representatives of the pharmaceutical industry rate patents as far more important to their continued innovation and survival than do representatives of any other area of industry.[36]

Additionally, patents are typically thought to be a key mechanism not only for encouraging companies to invest in developing expensive, risky technologies, but also for encouraging transactions of information between institutions. A university may want to license their technology to a company that would develop the product, or a small company may want to pitch its technology to a venture-capital firm. Arrow's famous information paradox explains the key difficulty with exchanging critical information without the protection of intellectual property: a piece of information's value "for the purchaser is not known until he has the information, but then he has in effect acquired it without cost."[37]

Patents are thought to provide a solution to this paradox by enabling inventors to disclose information about their inventions and enable transactions, while at the same time ensuring that the purchaser is legally prohibited from absconding with the relevant information.[38] To be sure, scholars have argued persuasively both that patents are not the only way of facilitating these transactions and that not all information is subject to Arrow's para-

terly Performance, FOOD & DRUG ADMIN., https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm600678.htm [https://perma.cc/2PE9-WDNQ] (last updated Aug. 3, 2018). See *infra* text accompanying notes 241–252 for an examination of the differences between the small-molecule drug context and the biologic drug context.

34. Burk & Lemley, *supra* note 1, at 1617; *see also, e.g.*, Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 720–21 (2005); Roin, *supra* note 2, at 751; Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 507–08 (2009) [hereinafter Roin, *Unpatentable Drugs*].

35. FED. TRADE COMM'N, *supra* note 1, at 14.

36. *See, e.g.*, Graham et al., *supra* note 28, at 1286; Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)* 2, 12 (Nat'l Bureau of Econ. Research, Working Paper No. 7552, 2000), http://www.nber.org/papers/w7552 [https://perma.cc/M8C5-LSCJ].

37. Kenneth J. Arrow, *Economic Welfare and the Allocation of Resources for Invention*, *in* THE RATE AND DIRECTION OF INVENTIVE ACTIVITY 609, 615 (Nat'l Bureau of Econ. Research ed., 1962); *see also* Ashish Arora & Robert P. Merges, *Specialized Supply Firms, Property Rights and Firm Boundaries*, 13 INDUS. & CORP. CHANGE 451, 454 (2004).

38. Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents–Prizes Debate*, 92 TEX. L. REV. 303, 335 (2013); Mark A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 TEX. L. REV. 989, 1050–51 (1997).

dox.[39] But at least some start-up firms cite the existence of patents as key to their ability to transact with larger firms or obtain capital, and venture-capital firms in at least some fields use the presence of patents among their potential pool of investments as a signaling tool.[40]

This aspect of patents may also be of key importance in the pharmaceutical field. Over the past two decades, the structure of the industry has changed dramatically. First, mergers have significantly decreased the number of large, traditional pharmaceutical firms that possess the capacity to develop a drug in-house from its inception to approval.[41] Second, in recent years pharmaceutical companies have dramatically increased the rate at which they in-license drug candidates, rather than develop them from scratch in-house.[42] Consequently, even these large companies that remain are increasingly interested in in-licensing compounds that have met certain milestones in smaller firms, rather than developing products fully in-house.[43] Many of these smaller firms must obtain venture-capital funding and successfully complete preclinical research before being acquired by one of the remaining large firms.[44] To the extent that patents are useful in enabling these acquisitions, the pharmaceutical space is experiencing a boom in this type of deal.

Yet patents are not the only innovation incentives operating to encourage pharmaceutical companies to identify new drug targets and bring innovative products to market. To fully appreciate the role that patents play in the development of new drugs, it is important to understand the time and manner in which they operate as complements to other innovation incentives.

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39. Michael J. Burstein, *Exchanging Information Without Intellectual Property*, 91 TEX. L. REV. 227 (2012).

40. Hannah Hottenrott et al., *Patents as Quality Signals? The Implications for Financing Constraints on R&D*, 25 ECON. INNOVATION & NEW TECH. 197, 198–200 (2015).

41. John L. LaMattina, *The Impact of Mergers on Pharmaceutical R&D*, 10 NATURE REVIEWS DRUG DISCOVERY 559, 559 (2011).

42. *Billion-Dollar Babies*, ECONOMIST (Nov. 28, 2015), http://www.economist.com/news/business/21679203-high-cost-rd-used-explain-why-drugs-giants-merge-and-why-they-must-charge (on file with the *Michigan Law Review*); *see also* LaMattina, *supra* note 41, at 559–60.

43. *See* LaMattina, *supra* note 41, at 559; *see also Billion-Dollar Babies*, *supra* note 42.

44. *See* Jonathan D. Rockoff, *Big Pharma, Short on Blockbusters, Outsources the Science*, WALL STREET J. (Dec. 6, 2016, 11:43 AM), http://www.wsj.com/articles/big-pharma-short-on-blockbusters-outsources-the-science-1481042583 (on file with the *Michigan Law Review*). In some cases, small biotech companies are funded by the large companies themselves, which then retain the option to purchase the company once it has completed particular, specified milestones. *See, e.g.*, *id.*

B. *Patents as Part of a Broader Innovation Ecosystem for Pharmaceuticals*

The long, expensive process of developing new pharmaceuticals typically benefits not only from robust patent protection but also from other innovation incentives that operate along the same development process. Appreciating the way in which new drugs are developed and how the actors operating at different stages of the process interact with innovation incentives is key to understanding the unique yet complementary role patents play in the development of new pharmaceuticals. Patents are but one of many parts in a broader innovation ecosystem.[45]

The process of drug development typically begins with basic research. This research may be quite early-stage, seeking to understand the biological basis for a given human disease, or it may be somewhat later-stage, seeking to disrupt a particular disease process in the hopes of treating or curing that disease.[46] Importantly, this research is often done in academic laboratories, not in-house at pharmaceutical companies (large or small), and it may be difficult to point to any single drug compound resulting from the work.[47] But basic research is nevertheless critical to pharmaceutical companies' efforts to develop drug targets thoughtfully and purposively.

Not only is basic research typically performed in the university context, but it is also chiefly funded by public entities, in the United States primarily by the National Institutes of Health (NIH).[48] This federal funding is the first of the key innovation incentives operating in the pharmaceutical area. Research at this stage is risky: it often fails to achieve its intended purpose, and any successful product may be more than a decade of costly research away. Perhaps more importantly, such research produces generalizable knowledge that is often viewed as a public good.[49] The federal government recognizes and appreciates that basic information about the process of disease ought to be available to all researchers and has prioritized it accordingly. The annual budget of the NIH is roughly $30 billion,[50] more than half of which goes toward what I refer to here as basic research.[51]

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45. *See generally* Hemel & Ouellette, *supra* note 38 (discussing, for instance, patents, prizes, grants, and tax incentives).

46. Mike Lauer, *NIH's Commitment to Basic Science*, NIH Extramural Nexus (Mar. 25, 2016), https://nexus.od.nih.gov/all/2016/03/25/nihs-commitment-to-basic-science/ [https://perma.cc/27V6-PCX5].

47. B. Michael Silber, *Driving Drug Discovery: The Fundamental Role of Academic Labs*, Sci. Translational Med. (May 5, 2010), http://stm.sciencemag.org/content/scitransmed/2/30/30cm16.full.pdf [https://perma.cc/UFR6-6GU6].

48. Lauer, *supra* note 46.

49. Nancy Gallini & Suzanne Scotchmer, *Intellectual Property: When Is It the Best Incentive System?*, 2 Innovation Pol'y & Econ. 51, 53–54 (2002).

50. Office of Budget, Nat'l Insts. of Health, History of Congressional Appropriations, Fiscal Years 2000–2018, at 1 (2018), https://officeofbudget.od.nih.gov/pdfs/FY19/Approp%20History%20by%20IC%20FY% 202000% 20-%20FY%202018.pdf [https://perma.cc/3BQR-L68U].

51. Lauer, *supra* note 46.

The next phase of drug development—drug discovery and preclinical testing—is often performed in-house at a pharmaceutical company.[52] But increasingly, companies are also funding collaborations with academia targeted toward this phase of development.[53] Alternatively, just under half of the NIH's budget goes to the broader category of "applied research,"[54] although not all of it goes to particular translational projects of this type.[55] Even for companies responsible for their own costs during this portion of the development process, it is relatively inexpensive and brief compared with the clinical trial process that follows it.[56]

It is typically during this phase—once a compound has been identified and its potential utility discovered but before human trials begin—that companies will begin building a patent portfolio around the drug candidate in question.[57] Companies must start filing patent applications early due to doctrinal requirements that may prevent patents from being filed much later in the development process.[58] Although patents now last twenty years from the date of filing,[59] it may be another decade before the drug makes it to market, if it ever does. Companies often rely on the exclusivity patents provide dur-

52. Importantly, I do not mean to suggest that all these activities must happen at the same company. As I discuss *infra*, these functions are increasingly being divided up between industry actors.

53. Betsy McKay, *HIV Cure Is Goal of Glaxo-UNC Chapel Hill Partnership*, WALL STREET J. (May 10, 2015, 10:06 PM), http://www.wsj.com/articles/partnership-takes-aim-at-curing-hiv-aids-1431309601 (on file with the *Michigan Law Review*); Brigid Sweeney, *In Era of Research Cuts, Romance Blossoming Much Earlier Between Universities and Big Pharma*, CRAIN'S CHI. BUS. (June 10, 2017, 7:00 AM), http://www.chicagobusiness.com/article/20170610/ISSUE01/170609858/in-era-of-research-cuts-romance-blossoming-much-earlier-between-universities-and-big-pharma [https://perma.cc/VN4Z-VXMA].

54. Lauer, *supra* note 46.

55. Although much of it certainly does, as most if not all NIH Institutes have subgroups focusing on translational research. There is also an entire Institute—the National Center for Advancing Translational Sciences—focused on research into development challenges as a whole. *See, e.g.*, *NIH Establishes National Center for Advancing Translational Sciences*, NAT'L INSTS. OF HEALTH (Dec. 23, 2011), https://www.nih.gov/news-events/news-releases/nih-establishes-national-center-advancing-translational-sciences [https://perma.cc/723U-KRM4]. Additional research is run through the NIH Clinical Center, where clinical trials are performed. NIH Clinical Ctr., *About the Clinical Center*, NAT'L INSTS. OF HEALTH (2016), http://clinicalcenter.nih.gov/about1.html [https://perma.cc/P87P-PMTB] (last updated July 19, 2018).

56. DiMasi et al., *supra* note 30, at 25.

57. Roin, *Unpatentable Drugs*, supra note 34, at 539.

58. *See, e.g.*, 35 U.S.C. § 102(a) (2012); Jacob S. Sherkow, *Patent Law's Reproducibility Paradox*, 66 DUKE L.J. 845, 850, 883 (2017). Of course, there are also costs to such an early filing system. *See* Christopher A. Cotropia, *The Folly of Early Filing in Patent Law*, 61 HASTINGS L.J. 65, 93–96 (2009).

59. 35 U.S.C. § 154(a)(2) (2012).

ing this premarket period to carry them through the expensive clinical-trial process.[60]

Pharmaceutical companies will often supplement their patent portfolios with trade-secret protection. Most commonly, they will keep manufacturing processes of various types as trade secrets.[61] Although companies could in theory obtain patents on these processes, they are often quite difficult to enforce,[62] and trade secrecy may prove more valuable over time. Importantly, this trade secrecy has different effects on the development of different types of drugs. Small-molecule drugs like aspirin are often simple to reverse engineer, which is why generic versions can come to market cheaply and easily.[63] But complex biologic drugs, like monoclonal antibodies used to treat cancer or autoimmune conditions like rheumatoid arthritis,[64] are far more difficult to make, and scholars have argued persuasively that keeping biologic manufacturing processes as trade secrets likely delays the development of biosimilar versions.[65]

The clinical-trial process is generally the longest, most expensive portion of the drug-development process due to the legal requirements to prove safety and efficacy.[66] On average, companies are likely to spend more than $300 million out of pocket[67] and take roughly eight years[68] to bring a product

60. Sherkow, *supra* note 58.

61. W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. Rev. 491, 532–39 (2014) [hereinafter Price, *Making Do in Making Drugs*]; Cohen et al., *supra* note 36, at 10.

62. Price, *Making Do in Making Drugs*, *supra* note 61, at 526.

63. W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 Iowa L. Rev. 1023, 1028 (2016).

64. As one example, Erbitux (cetuximab) is a monoclonal antibody approved by the FDA for the treatment of a number of different kinds of cancer. *See generally Cetuximab*, NIH Nat'l Cancer Inst., https://www.cancer.gov/about-cancer/treatment/drugs/fda-cetuximab [https://perma.cc/7CTW-MYN5] (last updated Mar. 9, 2018).

65. Price & Rai, *supra* note 63, at 1026–28.

66. Other areas even within the health technology space do not face these constraints. For instance, most diagnostics generally do not require clinical trials. *See* Rachel E. Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. Davis L. Rev. 1881, 1889–90 (2016); Food & Drug Admin., Discussion Paper on Laboratory Developed Tests (LDTs) 8–9 (2017), http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf [https://perma.cc/63ML-G8JZ]. As a result, patents may be less important in the diagnostics field. Sec'y's Advisory Comm. on Genetics, Health & Soc'y, U.S. Dep't of Health & Human Servs., Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests 1, 34 (2010), https://osp.od.nih.gov/wp-content/uploads/2013/11/SACGHS_patents_report_2010.pdf [https://perma.cc/QW3L-GE9Z] ("[T]he prospect of patent protection of a genetic research discovery does not play a significant role in motivating scientists to conduct genetic research.").

67. DiMasi et al., *supra* note 30, at 24. Importantly, this is the average out-of-pocket cost per investigational compound. Since most drugs fail even in clinical trials, DiMasi estimates the out-of-pocket costs per *approved* compound to be nearly $1 billion. *Id.* at 25.

68. *Id.* at 24.

through clinical trials. To be sure, these numbers vary widely by disease,[69] but these are the most significant expenditures incurred by pharmaceutical companies on their way to market. There is significant risk here, too. Most drugs fail, many even after making it all the way to the last phase of clinical trials, after their sponsors have already incurred the cost of development.[70]

Here, too, companies are not without support from the government. First, the federal government provides a series of tax benefits to companies incurring R&D costs. More general provisions like those permitting expensing of research costs or a tax credit for increasing R&D[71] are available broadly. But the government has also created special incentives for companies operating in areas where innovation incentives are viewed as likely to be low, such as orphan drugs. The Orphan Drug Act of 1983 enabled pharmaceutical companies to claim a 50% tax credit for clinical-trial expenses for drugs designed to treat rare diseases.[72]

The 2017 tax reform in Congress reduced the Orphan Drug clinical-trial tax credit to 25%,[73] giving credence to concerns expressed by scholars that nonpatent incentives may be more susceptible to political whims.[74] That is, pharmaceutical companies may be reticent to innovate primarily in reliance on nonpatent incentives, if they are perceived as more likely to be revised downward. Yet this is the first instance of a Congressional walk-back since Congress began creating these incentives in the early 1980s, and it was coupled with a significant decrease in the overall corporate tax rates from 35% to 21% and even lower one-time repatriation rates.[75] Although pharmaceutical companies may not be able to claim as large a credit for specific orphan-drug expenditures going forward, these other benefits may compensate these companies financially.[76]

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69. *See, e.g.*, *id.* at 32 (noting that diabetes drugs have shorter clinical development times than average); Aaron S. Kesselheim et al., *Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer*, 305 JAMA 2320, 2323 (2011) (noting that orphan drugs spent much less time in clinical trials than nonorphan drugs).

70. *See, e.g.*, Hay et al., *supra* note 32, at 40.

71. Hemel & Ouellette, *supra* note 38, at 321–36.

72. Orphan Drug Act, Pub. L. No. 97-414, § 4, 96 Stat. 2049, 2053–56 (1983); Hemel & Ouellette, *supra* note 38, at 378–79.

73. Act of Dec. 22, 2017, Pub. L. No. 115-97, § 13401, 131 Stat. 2054, 2133–34 ("Modification of Orphan Drug Credit").

74. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 366 (2007).

75. Daisuke Wakabayashi & Brian X. Chen, *Apple, Capitalizing on New Tax Law, Plans to Bring Billions in Cash Back to U.S.*, N.Y. TIMES (Jan. 17, 2018), https://www.nytimes.com/2018/01/17/technology/apple-tax-bill-repatriate-cash.html (on file with the *Michigan Law Review*).

76. Ryan Cross, *Drug Company Earnings Outlook Bolstered by Tax Cuts and Repatriated Cash*, CHEM. & ENG'G NEWS (Feb. 8, 2018), https://cen.acs.org/articles/96/i7/Drug-company-earnings-outlook-bolstered.html [https://perma.cc/BEH5-K9D4].

Second, companies developing innovative drugs for unmet medical needs can often avail themselves of different pathways to expedite the approval of their products.[77] These pathways—Fast Track, Breakthrough Designation, Accelerated Approval, and Priority Review—enable companies to shorten the time (and therefore the cost) spent in the clinical-trial process.[78] The pathways differ slightly in the information required to qualify for the program and in the benefits they provide, but designation under one of these programs can significantly benefit a drug sponsor. For instance, the Accelerated Approval program permits sponsors to obtain FDA approval on the basis of a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict the drug's clinical benefit,[79] perhaps greatly speeding up the clinical trial process.

Third, once a drug is approved by the FDA, its sponsor can then take advantage of one of the most valuable innovation incentives: an FDA-administered exclusivity period. Depending on the type of drug approved, companies will receive either five, seven, or twelve years of exclusivity to market their drug.[80] These exclusivity periods do differ legally in important aspects. The Orphan Drug Act confers *market* exclusivity on the makers of orphan drugs, such that the FDA will not approve the same drug for the same disease for a period of seven years.[81] The Hatch-Waxman Act and the Biologics Price Competition and Innovation Act, by contrast, confer *data* exclusivity and prevent the follow-on product from relying on the innovator company's data package for a period of time. Here, too, there are important differences. Hatch-Waxman exclusivity runs from the approval of the innovator product until the *filing* of the generic application,[82] while the Biologics Act exclusivity runs from the approval of the innovator product until the *approval* of the follow-on biosimilar.[83] Although to date these exclusivity periods have often behaved functionally interchangeably, it is possible the complexities of the biologics approval pathway will change these dynamics in the future.

77. For an overview and comparison of these four programs, see Center for Biologics Evaluation and Research & Center for Drug Evaluation and Research, Food & Drug Admin., Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics 7–8 (2014), http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf [https://perma.cc/5WJW-S28L].

78. *Id.*

79. 21 U.S.C. § 356(c)(1)(A) (2012).

80. *See, e.g.*, 21 U.S.C. § 355(j)(5)(F)(ii) (2012) (Hatch-Waxman Act, conferring a five-year period of exclusivity for small-molecule drugs); 21 U.S.C. § 360cc(a) (Orphan Drug Act, conferring seven years of market exclusivity); 42 U.S.C. § 262(k)(7)(A) (2012) (Biologics Price Competition and Innovation Act, conferring twelve years of data exclusivity).

81. 21 U.S.C. § 360cc(a).

82. *Id.* § 355(j)(5)(F)(ii).

83. 42 U.S.C. § 262(k)(7)(A); *see also id.* § 262(k)(7)(B) (noting that an application may not be filed for four years).

These exclusivity periods typically run in parallel with the patent life remaining on a drug after FDA approval,[84] and in some ways they offer even stronger protection than can be gained with a patent, even a primary patent. FDA exclusivity periods are automatically enforced against other companies, with the FDA standing as market gatekeeper, whereas patents require resources both to detect violations of the patents and to enforce the patents against such violations.[85] Further, FDA exclusivity periods are not meaningfully subject to challenge and invalidation in either the courts or administrative bodies[86] the way patents are.[87]

These different innovation incentives—federal funding for basic research, R&D tax credits, patents, trade secrecy, expedited approval pathways, and FDA exclusivity periods[88]—all act on different actors at different points in time to drive the drug development process forward.[89] Patents are just one piece of this puzzle, but they serve important and often unique functions. Most importantly, patents provide exclusive protection over a drug even before it comes to market, during the period when companies are investing hundreds of millions of dollars into clinical trials. Patents may also enable small companies to attract venture-capital funding or the interest of large companies who may seek to buy them or otherwise license their technology.[90] As large companies increasingly in-license compounds from small companies rather than develop them from scratch in-house, this feature of patents may become even more important. And as noted above, the fact that the patent clock starts early, years before FDA approval, can prevent potentially wasteful races.

To be sure, some functions of patents are duplicated by other innovation incentives. To the extent that FDA exclusivity periods and patents run concurrently after a drug is approved, patents may provide fewer benefits post-approval.[91] And companies may choose even during the development pro-

84. C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327, 330 (2012).

85. Heled, *supra* note 8, at 431.

86. *See* 35 U.S.C. § 311 (2012) (establishing the inter partes review process, allowing patents to be challenged and reviewed before the USPTO in a limited set of circumstances).

87. Heled, *supra* note 8, at 431–32.

88. There are more traditional nonlegal incentives that operate in this space as well—first-mover advantages are important for certain types of products, particularly for one-time vaccines or curative technologies, where there may be pent-up demand for a product. In general, however, they are less powerful relative to legal incentives in the pharmaceutical industry, whereas they dominate in other fields, such as software or business methods.

89. Professors Daniel Hemel and Lisa Ouellette have developed a helpful taxonomy that classifies innovation policy levers along a series of dimensions, including whether they are administered ex ante or ex post, who decides the size of the reward, and who pays for it. *See generally* Hemel & Ouellette, *supra* note 38.

90. *See supra* text accompanying notes 38–44.

91. *See* Heled, *supra* note 8, at 431.

cess to keep certain information as a trade secret rather than apply for a patent. But particularly during the clinical-trial process, patents still enable a level of information disclosure and certainty that other incentives may lack.

The relevance of each of these different innovation incentives may vary even within the pharmaceutical industry. As noted above, the Orphan Drug Act created special tax incentives and exclusivity periods for drugs treating conditions affecting small populations.[92] Companies developing biologic drugs receive longer FDA exclusivity periods than do companies developing small-molecule drugs, regardless of the particular disease involved.[93] Therefore, I turn now to the microbiome field in particular, presenting an overview of the field and considering how the innovation process is likely to play out there.

II. The Emerging Field of Microbiome Research

The microbiome is the community of microbes that lives within each of our bodies—the bacteria, viruses, and protozoa that exist in a symbiotic relationship with us, at least most of the time.[94] The microbiome's growing popularity with scientists, investors, and policymakers has led many to ask if we might cure disease not by administering standard medicines, many of which may achieve their goals while at the same time imposing harmful side effects, but rather by altering the balance of our bodies' own internal flora. This Part first provides an introduction to the expanding field of microbiome research before situating the microbiome in the context of Part I. Specifically, the same factors that lead scholars to place patents at the center of the typical innovation process in the pharmaceutical industry will lead them to give patents primacy here as well.

A. *Exploring the Microbiome*

Until just a few years ago, the microbiome was not a topic of mainstream scientific interest. But its popularity has exploded overnight. Not only have premier scientific publications like *Science* and *Nature* devoted entire issues to the topic,[95] but more popular press outlets like *Scientific American* and the *Economist* have been similarly riveted.[96] Even politicians have noticed: President Obama's creation of the BRAIN Initiative, Personalized

92. Orphan Drug Act, Pub. L. No. 97-414, § 4, 96 Stat. 2049, 2053–56 (1983).

93. *Compare* 21 U.S.C. § 355(j)(5)(F)(ii) (2012) (conferring a five-year period of exclusivity for small-molecule drugs), *with* 42 U.S.C. § 262(k)(7)(A) (2012) (conferring twelve years for biologic drugs).

94. Yong, *supra* note 4, at 2–3.

95. *See, e.g.*, Special Issue, *Microbiome*, 352 Science 530 (2016); *Innovations in the Microbiome*, Nature (Supplement) S1 (2015).

96. *See, e.g.*, *Special Report: Innovations in the Microbiome*, Scientific Am. (Feb. 17, 2015), https://www.scientificamerican.com/report/innovations-in-the-microbiome/ [https://perma.cc/9A7N-2Y3Y]; *Microbes Maketh Man*, Economist (Aug. 18, 2012), https://www.economist.com/node/21560559 [https://perma.cc/QQ6Q-V8C4].

Medicine Initiative, and Cancer Moonshot were widely covered, but he also launched a National Microbiome Initiative.[97]

Why the sudden focus on the microbiome in general, and the gut microbiome specifically? Chiefly, it has been linked to almost every disease you can think of. It has been linked to autoimmune disorders like diabetes and arthritis, mental health conditions like schizophrenia and depression,[98] and a range of conditions affecting our intestinal systems, including Crohn's disease and antibiotic-resistant infections.[99] Some of these links are stronger than others, but it is clear that the microbiome plays a key role in maintaining human health.

Perhaps the most advanced example of the microbiome's potential to affect our health is fecal microbiota transplantation, or FMT. FMT is a medical procedure in which stool is transferred from a healthy donor into the bowel of a patient. Over the last decade, interest in FMT as an effective nonantibiotic means to treat recurrent *Clostridium difficile* infections has surged. *C. difficile* is the most common hospital-acquired pathogen;[100] the number of infections it causes doubled between 2000 and 2005,[101] and hospitalizations due to these infections doubled between 2000 and 2010.[102] *C. difficile* causes over 450,000 new infections,[103] 250,000 hospitalizations, and around 14,000 to 29,000 deaths in the United States each year,[104] and it is estimated to cost the U.S. healthcare system around $4.8 billion annually.[105] Due to the rise of

97. Jo Handelsman, *Announcing the National Microbiome Initiative*, White House (May 13, 2016, 6:00 AM), https://obamawhitehouse.archives.gov/blog/2016/05/13/announcing-national-microbiome-initiative [https://perma.cc/95ZY-F4BX].

98. *See, e.g.*, Jane E. Brody, *Unlocking the Secrets of the Microbiome*, N.Y. Times (Nov. 6, 2017), https://www.nytimes.com/2017/11/06/well/live/unlocking-the-secrets-of-the-microbiome.html (on file with the *Michigan Law Review*); *Microbes Maketh Man*, *supra* note 96; *Special Report: Innovations in the Microbiome*, *supra* note 96.

99. Dirk Gevers et al., *The Treatment-Naïve Microbiome in New-Onset Crohn's Disease*, 15 Cell Host & Microbe 382 (Mar. 12, 2014).

100. Shelley S. Magill et al., *Multistate Point-Prevalence Survey of Health Care–Associated Infections*, 370 New Eng. J. Med. 1198, 1198 (2014).

101. In 2005, there were 11.2 cases of *C. difficile* infection per 10,000 inpatient hospitalizations. Marya D. Zilberberg et al., *Increase in Adult* Clostridium difficile*–Related Hospitalizations and Case-Fatality Rate, United States, 2000–2005*, 14 Emerging Infectious Diseases 929, 929 (2008).

102. Fernanda C. Lessa, et al., *Burden of* Clostridium difficile *Infection in the United States*, 372 New Eng. J. Med. 825, 826 (2015).

103. *Id.* at 828.

104. *Id.* at 829; The White House, National Action Plan for Combating Antibiotic-Resistant Bacteria 60 (2015), https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf [https://perma.cc/XA85-E49D].

105. *See* Erik R. Dubberke & Margaret A. Olsen, *Burden of* Clostridium Difficile *on the Healthcare System*, 55 Clinical Infectious Diseases S88, S88 (2012). Of course, this is to say nothing of the additional burden on families and caregivers, which is certainly substantial as

antibiotic resistance among pathogens, not all patients with a *C. difficile* infection will respond to traditional antibiotic therapies. But the cure rate for patients who experience two or more recurrences of *C. difficile* infection and obtain a fecal transplant is 90%—far beyond the 30–40% chance of success with standard antibiotics.[106]

As yet, microbiome-based treatments have demonstrated less success in preliminary trials for other conditions. Many of these studies serve as important reminders of how much we have yet to learn about the microbiome. For instance, one recent randomized, placebo-controlled trial of FMT's use in ulcerative colitis showed moderate efficacy overall, but nearly all that efficacy was traceable to patients receiving samples from a single donor.[107] Patients receiving samples from other donors did not have as good clinical outcomes on average.[108] It is not yet known why this donor's stool is particularly effective at treating patients with ulcerative colitis, but scientists are continuing to study the question.[109]

Industry's interest in the field of microbiome research has similarly grown tremendously in recent years. In 2011, there were just two products in active development that would modulate the microbiome.[110] By 2017, there were 70.[111] There are now more than two dozen small companies operating in this space, and several larger companies have entered into licensing agreements or acquisition deals with small companies to move products forward through the FDA approval process.[112] Many of these drug candi-

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well. *See generally* S.M. McGlone et al., *The Economic Burden of* Clostridium difficile, 18 Clinical Microbiology & Infection 282 (2012) (modeling costs of *Clostridium difficile* while taking such burdens into account.

106. Gauree G. Konijeti et al., *Cost-Effectiveness of Competing Strategies for Management of Recurrent* Clostridium difficile *Infection: A Decision Analysis*, 58 Clinical Infectious Diseases 1507, 1511 (2014).

107. Paul Moayyedi et al., *Fecal Microbiota Transplantation Induces Remission in Patients with Active Ulcerative Colitis in a Randomized Controlled Trial*, 149 Gastroenterology 102, 105 (2015).

108. *Id.*

109. *See* Ari M. Grinspan & Colleen R. Kelly, Editorial, *Fecal Microbiota Transplantation for Ulcerative Colitis: Not Just Yet*, 149 Gastroenterology 15, 17 (2015).

110. Hannah Sally, Microbiome Modulator Drugs–The New Generation of Therapeutic 2 (2018), https://pharmaintelligence.informa.com/~/media/Informa-Shop-Window/Pharma/Whitepapers/Pharmaprojects-Microbiome-Whitepaper.pdf [https://perma.cc/2WHW-NTUU].

111. *Id.*

112. *Id.* at 3–4; Ben Adams, *Finch Therapeutics, Takeda Ink New Microbiome GI Collab*, FierceBiotech (Apr. 5, 2017, 7:00 AM), http://www.fiercebiotech.com/biotech/finch-therapeutics-takeda-ink-new-microbiome-gi-collab [https://perma.cc/93X9-NQTP]; John Carroll, *J&J Takes Another Leap into Microbiome R&D with $241M Vedanta Pact*, FierceBiotech (Jan. 13, 2015, 9:08 AM), http://www.fiercebiotech.com/partnering/j-j-takes-another-leap-into-microbiome-r-d-241m-vedanta-pact [https://perma.cc/D964-JZ2G]; Brittany Meiling, *Ferring Buys Up PhIII Microbiome Drug with Acquisition of Rebiotix*, Endpoints News (Apr. 5, 2018, 9:30 AM), https://endpts.com/ferring-buys-up-phiii-microbiome-drug-with-acquisition-of-rebiotix/ [https://perma.cc/DAG7-QA5X].

dates (13) are being developed for the treatment of *C. difficile* infection,[113] but other candidates are being developed for the treatment of a range of gastrointestinal disorders (including ulcerative colitis), metabolic indications, and dermatological conditions.[114] There are also several products at the preclinical stage targeted at different cancers.[115]

We should all want scientists and companies to investigate links between the microbiome and other diseases and to look to develop microbiome-based treatments for them. And to encourage scientists and companies to conduct this research, it is critical to find the right balance of innovation incentives.

B. *Microbiome-Based Technologies as Pharmaceuticals*

The FDA has chosen to regulate microbiome-based therapies as biologic drugs.[116] Importantly, this was not obviously required by existing statutes and regulations.[117] I and others have argued that fecal transplants in particular ought to be regulated under the FDA's paradigm for regulating human tissues like blood.[118] When regulating tissues, the FDA requires more stringent safety regulation and less stringent efficacy regulation before a product may come to market. Many of the most important public health questions the agency faces in regulating fecal transplantation—including the need to make sure communicable diseases are not transmitted through the process—are more akin to the questions the agency faces in regulating tissues and are not really contemplated by the standard pharmaceutical regulatory paradigm.[119]

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113. SALLY, *supra* note 110, at 7.

114. *Id.* at 9, 12, 14.

115. *Id.* at 14–15.

116. Rachel E. Sachs & Carolyn A. Edelstein, *Ensuring the Safe and Effective FDA Regulation of Fecal Microbiota Transplantation*, 2 J.L. & BIOSCIENCES 396, 398 (2015). The FDA's reason for doing so was not made public. However, a co-author and I have considered two possible reasons for their decision. *Id.* at 410–12. It is unlikely that either of these reasons, which hinge on the character of the cells as microbial rather than purely human, would be of concern to companies in nonmicrobiome therapeutic areas.

117. *See* 21 U.S.C. § 321(g)(1) (2012) (defining "drug"); 42 U.S.C. § 262(i)(1) (2012) (defining "biological product"); 21 C.F.R. § 1271.3(d)(3) (2017) (defining human cells and tissues).

118. Diane Hoffmann et al., *Improving Regulation of Microbiota Transplants*, 358 SCI. 1390, 1391 (2017); Sachs & Edelstein, *supra* note 116, at 398; Mark B. Smith et al., *Policy: How to Regulate Faecal Transplants*, 506 NATURE 290, 290 (2014).

119. Sachs & Edelstein, *supra* note 116, at 398. The statutory definitions the agency is working with are decades old, and they do not adequately contemplate modern technological advances not only in microbiome research but in other fields as well, such as 3-D bioprinting and mobile health. *See generally* Jody Freeman & David B. Spence, *Old Statutes, New Problems*, 163 U. PA. L. REV. 1 (2014).

The FDA's decision to regulate microbiome-based therapies as biologic drugs has a number of effects on the development process for these therapies going forward. First, it means that companies in this field must proceed through the standard clinical-trial process before their products can come to market. They must incur the costs and risks of the approval process, those that we think make patent protection necessary for companies developing such drugs. Second, it means that these products are eligible for the suite of additional innovation incentives that have been created around drugs. At least two companies have already received both breakthrough-therapy designations[120] and orphan-drug designations for their microbiota-based candidates.[121] Not only will their clinical-trial process be accelerated, but also upon approval they can look forward to receiving the seven years of market exclusivity that comes with orphan-drug approval and twelve years of biologic drug data exclusivity.[122]

In short, the FDA is attempting to impose a conventional set of rules—both restrictions and benefits—on an unconventional set of products. And the FDA is dealing with the incongruities between these technologies and the clinical trial approval process as best as it can. But not every area of the law will adapt quite so easily. In particular, although the FDA may see these products as drugs, the patent system may not—a potential problem to which I now turn.

III. Obstacles to Patenting Microbiome-Based Therapies

If patents are necessary for the development and commercialization of microbiome-based therapies, then scientists and companies may be in trouble. In this Part, I argue that microbiome-based therapies cannot be patented under current doctrine in the same way that other pharmaceuticals can be patented. After analogizing the types of claims that would be relevant in both situations, I draw on patent-law doctrine and an examination of granted patents to argue that the doctrines of patent-eligible subject matter under 35

120. *Rebiotix Receives Breakthrough Therapy Designation for RBX2660*, Rebiotix (Oct. 12, 2015), http://www.rebiotix.com/news-media/press-releases/rebiotix-receives-breakthrough-therapy-designation-for-rbx2660-recurrent-c-diff/ [https://perma.cc/XHT2-KYEB]; *Seres Therapeutics Receives FDA Breakthrough Therapy Designation for Its Lead Product Candidate, SER-109*, BusinessWire (June 12, 2015, 7:32 AM), https://www.businesswire.com/news/home/20150612005297/en/Seres-Therapeutics-Receives-FDA-Breakthrough-Therapy-Designation [https://perma.cc/MY7K-6KRV].

121. *Orphan Drug Designation for "Fecal Microbiota" Granted to Rebiotix*, Food & Drug Admin., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=421013 [https://perma.cc/Q957-E542] (granted Mar. 10, 2014); *Orphan Drug Designation for "Encapsulated Spores from Fecal Microbiota" Granted to Seres*, Food & Drug Admin., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=466214 [https://perma.cc/8FZC-XH2X] (granted Aug. 19, 2015); *Orphan Drug Designation for "Alloegeneic Fecal Microbiota" Granted to MaaT Pharma*, Food & Drug Admin., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=627418 [http://perma.cc/RL3Y-JPQ8] (granted Feb. 28, 2018).

122. 21 U.S.C. § 360cc(a) (2012); 42 U.S.C. § 262(k)(7)(A) (2012).

U.S.C. § 101 and enablement and written description under 35 U.S.C. § 112 are preventing companies from obtaining the most valuable patents on microbiome-based therapies. I also consider more practical barriers to enforcement of such patents even where they do exist.

A. *Analogizing Microbiome-Based Therapies to Traditional Pharmaceutical Products*

When traditional pharmaceuticals receive FDA approval and come to market, they are usually protected by a handful of patents.[123] Scholars often group these patents into two categories, with "primary" patents (those covering the chemical compound itself) being the most valuable, and "secondary" patents (those covering everything else about a drug) being less valuable but still significant for companies.[124] Although they are not equally important to pharmaceutical companies, any given drug is typically protected by both types of patents.

The big prize for any pharmaceutical company is the primary patent on a drug compound. Primary patents are far more important than secondary patents because they can be used to prevent any other company from making and selling the compounds they claim, even if another company has discovered entirely new uses for them. Consider as an example Crestor, a blockbuster statin for the treatment of high cholesterol.[125] Its developers obtained a patent on the core compound making up Crestor (rosuvastatin),[126] preventing competitors from making and selling that compound for any purposes—even if they discovered a secondary use for it.

Secondary patents can cover everything from particular formulations of a drug (such as whether it will be made in tablet versus injectable form), to

123. Lisa Larrimore Ouellette, Note, *How Many Patents Does It Take to Make A Drug? Follow-on Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299, 300 (2010). A smartphone, by contrast, may be covered by thousands or even hundreds of thousands of patents. Anup Malani & Jonathan S. Masur, *Raising the Stakes in Patent Cases*, 101 GEO. L.J. 637, 679 n.155 (2013).

124. María José Abud et al., *An Empirical Analysis of Primary and Secondary Pharmaceutical Patents in Chile*, 10 PLOS ONE e0124257 (2015), http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124257 [https://perma.cc/77CA-2HHL]; Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PLOS ONE e49470 (2012), http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049470 [https://perma.cc/7LQ9-BFPU].

125. *See generally Orange Book Patent and Exclusivity for N021366*, FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=002&Appl_No=021366&Appl_type=N [https://perma.cc/KR6G-SP4W] (disclosing five distinct patents on Crestor); Andrew Pollack, *AstraZeneca Pushes to Protect Crestor From Generic Competition*, N.Y. TIMES (June 27, 2016), https://www.nytimes.com/2016/06/28/business/astrazeneca-pushes-to-protect-crestor-from-generic-competition.html (on file with the *Michigan Law Review*) ("Crestor is the company's best-selling drug, accounting for $5 billion of its $23.6 billion in product sales last year.").

126. U.S. Patent No. 6,316,460 (issued Nov. 13, 2001).

method of treatment or use claims, to claims covering modified versions of the relevant compound.[127] Take Crestor again. It is also covered by four secondary patents, on methods of using rosuvastatin to treat particular types of high cholesterol,[128] on diagnostic tools to encourage the use of rosuvastatin,[129] and on chemical derivatives of the core molecule.[130] Secondary patents covering methods of using particular compounds to treat particular conditions are less valuable than primary patents largely because of the difficulties inherent in enforcing them, as discussed *infra*.[131] Scholars have written about the particular problems of enforcing patents on new uses for old drugs, in large part because these patentholders cannot easily prevent a generic product approved for the original indication from being prescribed and substituted for the drug's new use.[132]

In the context of microbiome-based therapies, though, it is not quite so easy to define the "compound" that would be protected by a primary patent. That is, describing the microbiome "compound" is much more complicated than reciting the chemical structure of a small-molecule drug like Crestor. Consider FMT again as an example. For some companies operating in this space, the "compound" is simply whole filtered stool.[133] For others, it is a combination of particular bacteria that is administered to a patient.[134] A few companies in this space are even contemplating traditional small-molecule approaches to treatment.[135]

Secondary patents in the microbiome context may look more like their traditional small-molecule analogues. These patents might claim methods of processing, packaging, and delivering the relevant products, particular formulations thereof, or methods of using microbiome-based therapies to prevent or treat conditions ranging from *C. difficile* infections to Crohn's disease to depression. Again, these will likely be less valuable than patents on the relevant "compounds," but still important to companies operating in this space.

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127. *See* Kapczynski et al., *supra* note 124.

128. U.S. Patent No. 6,858,618 (issued Feb. 22, 2005).

129. U.S. Patent No. 7,030,152 (issued Apr. 18, 2006); U.S. Patent No. 7,964,614 (issued June 21, 2011).

130. U.S. Patent No. RE 37314 (reissued Aug. 7, 2001).

131. *See infra* Section III.C.

132. Eisenberg, *supra* note 34, at 722.

133. *See, e.g.*, *About*, OpenBiome, http://www.openbiome.org/about [https://perma.cc/MMQ6-CGBJ].

134. *See, e.g.*, Mark Ratner, *Microbial Cocktails Join Fecal Transplants in IBD Treatment Trials*, 33 Nature Biotechnology 787, 787 (2015).

135. *See, e.g.*, *Drug Discovery Platform*, Second Genome, http://www.secondgenome.com/platform/platform [https://perma.cc/27M5-GWJD].

B. *Doctrinal Barriers to Patenting*

A series of doctrinal barriers exist for companies seeking primary "compound" patents on microbiome-based therapies. Specifically, the doctrines of patent-eligible subject matter under 35 U.S.C. § 101 and enablement and written description under 35 U.S.C. § 112 will, in the typical case, prevent companies from obtaining such patents. Importantly, my arguments below are not merely based on case law—they are supplemented with information from public searches, as I describe in Section III.D *infra*.

The primary barrier to obtaining "compound" patents on microbiome-based therapies is 35 U.S.C. § 101, the requirement that claims cover patent-eligible subject matter.[136] Not every claim satisfying the substantive requirements of patent law—novelty, nonobviousness, and the disclosure requirements—may be patented. The Supreme Court has articulated a number of categories which are not eligible for patent protection, including "[l]aws of nature, natural phenomena, and abstract ideas."[137] As Justice Breyer explained, the justification for these exclusions is not that such exclusions are "obvious, or that their discovery is easy, or that they are not useful . . . . Rather, the reason for the exclusion is that sometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts.'"[138]

Although no court has yet confronted the question of patent-eligibility of microbiome-based therapies specifically, § 101 litigation often focuses on the meaning of these exclusions and on factual analogies to past precedent. In the microbiome context, one precedent stands out: *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, a 1948 Supreme Court case.[139] *Funk Brothers* involved a patent claiming a combination of different strains of *Rhizobium* bacteria, which help fix nitrogen from the air and enable plants to grow.[140] Previously, farmers had to purchase fertilizers containing separate strains for each type of crop they wanted to fertilize, because it was thought that different species of *Rhizobium* inhibited each other when mixed.[141] The inventor's insight here was that only some species inhibit each other, and so some

136. This Section provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101 (2012).

137. Alice Corp. v. CLS Bank Int'l, 134 S. Ct. 2347, 2354 (2014); Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 70–71 (2012); Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).

138. Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., 548 U.S. 124, 126 (2006) (Breyer, J., dissenting from dismissal of certiorari) (quoting U.S. CONST. art. I, § 8, cl. 8).

139. 333 U.S. 127 (1948).

140. *Funk Bros. Seed Co.*, 333 U.S.. at 129; U.S. Patent No. 2,200,532, claim 4 (issued May 14, 1940).

141. *Funk Bros. Seed Co.*, 333 U.S. at 129–30.

strains could in fact be used in mixed cultures on different varieties of crops.[142]

The Supreme Court invalidated the patent on the combination of *Rhizobium* strains.[143] Justice Douglas concluded that all the patentee had done was to "[d]iscover[] . . . the fact that certain strains of each species . . . can be mixed without harmful effect."[144] And because that discovery and the subsequent combination of the bacteria "produces no new bacteria" and "[e]ach species has the same effect it always had," the patentee had not satisfied the patent statute's requirement of "invention."[145] "For patents cannot issue for the discovery of the phenomena of nature. The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none."[146] Importantly, Justice Douglas acknowledged that the combination was clearly new and useful to farmers. But, still, that was not enough for the Court.[147]

Funk Brothers is an old case. In 1948, the justices could not have appreciated the types of technologies under investigation today by companies studying the microbiome. The case even predates the 1952 Patent Act, and therefore it doesn't (and can't) reference concepts like patent-eligible subject matter.[148] But *Funk Brothers* is still good law. The Supreme Court and Federal Circuit continue to cite and discuss *Funk Brothers* extensively in § 101 cases,[149] and there is no evidence Congress intended to abrogate the case, either in 1952 or since.[150]

Perhaps more importantly, the broader principle that products of nature standing alone are not eligible for patent protection remains strong. Since 2010, the Supreme Court and Federal Circuit have decided a series of key cases striking down such patents on § 101 grounds. Most pertinently, the Supreme Court, in *Ass'n for Molecular Pathology v. Myriad Genetics*, examined the reach of the "products of nature" exception and concluded that iso-

142. *Id.* at 130.

143. *Id.* at 132.

144. *Id.* at 131.

145. *Id.*

146. *Id.* at 130 (citation omitted).

147. *Id.* at 131.

148. *Id.* Some scholars view *Funk Brothers* as a case fundamentally about obviousness under 35 U.S.C. § 103. *See generally* Shine Tu, Funk Brothers—*An Exercise in Obviousness*, 80 UMKC L. Rev. 637 (2012). However, the courts themselves view it as a § 101 case and most scholars analyze it in this way. *See, e.g.*, Jeffrey A. Lefstin, *Inventive Application: A History*, 67 Fla. L. Rev. 565, 628 (2015).

149. *See, e.g.*, Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 591 (2013); Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 71–72 (2012); Bilski v. Kappos, 561 U.S. 593, 602 (2010); Diamond v. Chakrabarty, 447 U.S. 303, 310 (1980); Ariosa Diagnostics, Inc. v. Sequenom, Inc., 809 F.3d 1282, 1288–89 (Fed. Cir. 2015); *In re* Roslin Inst. (Edinburgh), 750 F.3d 1333, 1336 (Fed. Cir. 2014).

150. *See generally* Lefstin, *supra* note 148.

lated DNA sequences are products of nature and therefore not patent-eligible.[151] *Mayo v. Prometheus*[152] and *Ariosa v. Sequenom*[153] have gone on to invalidate diagnostic-method patents on the grounds that the patents were claiming mere "laws of nature."[154] These cases have made it hard—perhaps even impossible—to protect diagnostic technologies.[155] And in 2014, the Supreme Court, in *Alice Corp. v. CLS Bank*,[156] established a broad framework for evaluating questions of patent-eligibility,[157] which has since been used by federal courts to invalidate thousands of claims in more than 300 published decisions.[158]

Taken together, this analysis would seem to prevent innovators from obtaining primary "compound" patents on microbiome-based therapies, at least for those that claim simple combinations of bacterial strains. They are mere "products of nature," discovered but not invented. Like the claims in *Funk Brothers* and even *Myriad*, these combinations of strains may have very clear utility in diagnosing or treating disease, especially when compared to our prior knowledge of the microbiome's operation, and it may have been expensive to discover their functions. But the scientists have not created anything not found in nature already.[159]

Given these doctrinal obstacles to obtaining primary-product patents on microbiome-based therapies, companies in this space may be more likely to apply for claims covering methods of using particular bacterial strains or combinations thereof to treat disease.[160] These claims, however, face yet another barrier to patentability: the written description and enablement re-

151. *Myriad*, 569 U.S. at 596.

152. *Mayo*, 566 U.S. 66.

153. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015).

154. *Mayo*, 566 U.S. at 71–73; *Ariosa*, 788 F.3d at 1373.

155. *See, e.g.*, Rebecca S. Eisenberg, *Diagnostics Need Not Apply*, 21 B.U. J. Sci. & Tech. L. 256, 257 (2015); John M. Golden, Flook *Says One Thing,* Diehr *Says Another: A Need for Housecleaning in the Law of Patentable Subject Matter*, 82 Geo. Wash. L. Rev. 1765, 1791–92 (2014).

156. Alice Corp. v. CLS Bank Int'l, 134 S. Ct. 2347 (2014).

157. *Id.* at 2355.

158. *#AliceStorm: April Update and the Impact of TC Heartland on Patent Eligibility*, BilskiBlog (June 1, 2017), http://www.bilskiblog.com/blog/2017/06/alicestorm-april-update-and-the-impact-of-tc-heartland.html [https://perma.cc/CH6B-WDGU].

159. Of course, it is possible that the courts would ignore these past precedents and find these patents valid, if presented with such a case. The Supreme Court's compromise in the *Myriad* case, in which the justices held that isolated DNA sequences were not patent-eligible but cDNA sequences were eligible, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 580 (2013), suggests they might be concerned about innovation and receptive to such a possibility. The Court's denial of certiorari in the *Ariosa v. Sequenom* case, however, points in the other direction here. Sequenom, Inc. v. Ariosa Diagnostics, Inc., 136 S. Ct. 2511 (2016) (denying certiorari).

160. As I will detail in the next Part, several companies have not been awarded or even filed for any patents at all.

quirements of 35 U.S.C. § 112(a). Specifically, patents must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same."[161] Written description and enablement are two separate legal requirements,[162] and both may be challenged by the practicalities of patenting microbiome-related technologies.

The written-description requirement ensures that a patentee has not attempted to claim an invention more broadly than she actually possesses and that she has sufficiently disclosed her invention to the public.[163] This requirement is sometimes difficult to satisfy for patents in the life sciences, as they confront what is known as the genus–species problem. Specifically, patentees often attempt to claim a class (or genus) of compounds rather than a single specific compound, and cases often ask whether the inventor possessed a sufficient or sufficiently representative number of compounds (the species) within that class to pass muster.[164]

In the microbiome context, this genus–species problem may be quite literal. The *Funk Brothers* patent might fail today's written-description requirement for merely reciting strains of bacteria belonging to the genus *Rhizobium* without specifying particular species therein. Similarly, researchers today seeking to protect technologies involving strains from the genus *Lactobacillus* or *Bacteroides* cannot claim all such species.[165] Instead, they must disclose particular species and likely also describe their functional characteristics, each of which, of course, narrows the patent's scope. Both disclosures may even be required, because patentees who merely disclose particular species within a bacterial genus may find themselves facing enablement problems.

Patentees must not only describe their inventions. They must also enable others to make and use the invention without undue experimentation.[166] Although it is always difficult to determine what would qualify as "undue" in this context,[167] microbiome researchers know well that simply naming a genus and species of bacteria is insufficient to enable another researcher to use that strain. Strains of *Lactobacillus casei* isolated from different donors may

161. 35 U.S.C. § 112(a) (2012).

162. Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1340 (Fed. Cir. 2010) (en banc).

163. 35 U.S.C. § 112(a); *Ariad*, 598 F.3d at 1351.

164. *Ariad*, 598 F.3d at 1349–50; Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997).

165. Scientists have linked these genus to particular conditions within the gut microbiome. *See, e.g.*, Alexander Khoruts et al., *Changes in the Composition of the Human Fecal Microbiome After Bacteriotherapy for Recurrent* Clostridium difficile*-Associated Diarrhea*, 44 J. CLIN. GASTROENTEROLOGY 354, 354 (2010).

166. *Ariad*, 598 F.3d at 1352.

167. *See, e.g.*, *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988) ("Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.").

behave entirely differently, expressing different molecules in different amounts and possessing different disease-fighting abilities.[168] Consequently, even those holding method patents over bacterial strains have typically deposited samples of those strains with the PTO to satisfy the enablement requirement.[169]

Thus, even where companies obtain such method claims, they will face additional practical difficulties enforcing their patents, a topic to which I now turn.

C. *Practical Barriers to Enforcement*

Even if companies are able to obtain patents covering methods of administering their microbiome-based therapies, they will likely face difficulties enforcing them. First, they are likely to have difficulties searching for and locating potential infringers. Second, infringers are likely to be physicians or patients, and, as such, unattractive targets for infringement suits. These problems are certainly not unknown either to patent scholars or to companies in this area. Yet they have arisen less frequently in the pharmaceutical industry than in other fields of technology, and thus they may exacerbate an already difficult situation.

First, companies holding patents on methods of administering microbiome-based therapies may find it difficult to search for and identify potential infringers. The reason is quite simple: at least at present, standard fecal transplants have a do-it-yourself quality. Intrepid patients can perform these procedures in the privacy of their own home, with patient support groups providing step-by-step instructions and discussions of best practices for mixing stool in a low-cost blender and administering it via enema.[170] Even for patients who prefer the involvement of a physician, it may not be necessary to purchase the relevant product from a pharmaceutical company in the way that it is necessary for small-molecule drugs or other biologics. Thus, because of the ease of administration, patentholders cannot hope to locate each of these possibly infringing patients and physicians.

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168. *See* Michael McCarthy, *Genetically Identical Bacteria Can Behave in Radically Different Ways*, Univ. Wash.: UW News (Dec. 31, 2013), http://www.washington.edu/news/2013/12/31/genetically-identical-bacteria-can-behave-in-radically-different-ways/ [https://perma.cc/8S3G-33XD].

169. Ajinomoto Co. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1346 (Fed. Cir. 2000); *see, e.g.*, U.S. Patent No. 9,040,302 col. 19 ll. 11–40 (issued May 26, 2015).

170. *See, e.g.*, Emily Eakin, *The Excrement Experiment*, New Yorker (Dec. 1, 2014), https://www.newyorker.com/magazine/2014/12/01/excrement-experiment [https://perma.cc/3P5J-46ZQ]. Instructional guides produced by nonprofessionals and posted on YouTube have received tens of thousands of views. *See, e.g.*, HomeFMT, *Fecal Transplant (FMT)*, YouTube (May 13, 2013), http://www.youtube.com/watch?v=xLIndT7fuGo.

This problem of high search and enforcement costs for patentholders is not one typically confronted by pharmaceutical companies.[171] Precisely because the FDA acts as a powerful market gatekeeper, branded drug companies have the luxury of exerting little effort in identifying companies that may be infringing their primary-product patents. The patentholders can simply wait for generic companies to file for FDA approval[172] and declare them as potential infringers, because companies are not permitted to produce and sell drugs without the imprimatur of FDA approval. And patients and physicians typically do not make pharmaceutical products in their bathrooms at home, as they can with the ingredients for FMT.

Second, even if companies holding these method claims can identify potential infringers, they may be forced to sue physicians or patients for infringement, rather than other pharmaceutical companies.[173] Pharmaceutical companies do not want to be in the business of suing their customers. The financial and reputational harms are likely to be severe, and companies have generally avoided such behavior in the past. To be sure, physicians and patients are often the direct infringers of method claims. But their behavior can typically be attributed to those of other pharmaceutical companies selling the products as inducers of the infringement.[174] In this case, to the extent that patients and physicians are choosing the DIY option,[175] there is no such company to sue.

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171. To be sure, pharmaceutical companies have faced related problems in the past. As Professor Nicholson Price has argued, companies rely on trade secrets rather than patents in the context of pharmaceutical manufacturing techniques in large part because of the difficulties involved in enforcing such patents. Price, *Making Do in Making Drugs*, *supra* note 61, at 526, 532–39. But in such a case, the universe of potentially infringing parties is known and finite. In general, this problem has been more acute in other technological fields.

172. Here I am referring to the practice of filing Paragraph IV ANDAs. *See generally Patent Certifications and Suitability Petitions*, Food & Drug Admin., https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm047676.htm [https://perma.cc/7R6Z-3UML] (last updated Aug. 30, 2018).

173. It is unlikely that 35 U.S.C. § 287(c) (2012) will prevent the majority of such suits against physicians. Although § 287(c) exempts "medical practitioner[s]" and "related health care entit[ies]" from infringement liability for their "performance of a medical activity" that may nevertheless infringe a patent, the statute goes on to define "medical activity" as excluding patents on uses of compositions of matter, which predominate in the microbiome area. See Cynthia M. Ho, *Patents, Patients, and Public Policy: An Incomplete Intersection at 35 U.S.C. § 287(c)*, 33 U.C. Davis L. Rev. 601, 637–41 (2000), for analysis of the legal issues involved, and see generally Leisa Talbert Peschel, *Revisiting the Compromise of 35 U.S.C. § 287(c)*, 16 Tex. Intell. Prop. L.J. 299 (2008), for a review of the legislative history behind the provision.

174. *See* 35 U.S.C. § 271(b) (providing for induced infringement liability); Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 845 F.3d 1357, 1362–63, 1368–69 (Fed. Cir. 2017).

175. Indeed, the FDA is considering a guidance document that would permit hospitals to create and maintain stool banking facilities for just this purpose even after companies win FDA approval for related products. Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies; Draft Guidance for Industry; Availability, 81 Fed. Reg. 10,632, 10,633 (Mar. 1, 2016).

D. *The Existing Patent Landscape*

Importantly, these arguments above are not merely speculative. A search of all granted patents[176] that contain the terms "microbiome," "microbiota," or "fecal transplantation," has helped confirm these analyses. Although there are more than seventeen hundred granted patents where one of these terms appears somewhere in the patent, there are fewer than three hundred patents that are relevant to the discussion at hand.[177] The resulting patents were classified by category. Particularly relevant claims cover compositions of matter, including bacterial compounds, genetically modified bacteria, and standard drugs (either small-molecule or biologic) whose function is to modulate the microbiome, as well as methods.[178]

Sixty-three patents contain claims structured to mirror the kinds of core compound claims found in the small-molecule space. Most of these, however, do not claim microbes or combinations thereof in the *Funk Brothers* sense.[179] The vast majority claim formulations of compounds that look more like secondary-formulation patents that would be observed in the small-molecule space. For instance, U.S. Patent No. 9,682,108 does not simply claim "a plurality of viable non-pathogenic or attenuated pathogenic *Clostridium* spores, a plurality of viable nonpathogenic or attenuated pathogenic

176. The search was primarily conducted in Westlaw, searching for all granted U.S. patents containing the terms "microbiome," "microbiota," or "fecal transplantation." The search was first conducted in the summer of 2017, looking individually for all patents that had been granted up until that point and assessing their relevance. The search has been updated every month since then, again looking individually at granted patents. For purposes of this article, the search was last updated on September 1, 2018.

177. The vast majority of such patents merely mention the term "microbiome" once or twice in the specification, or the term appears in the title of a supporting reference, but the patent does not actually claim technologies that are in the relevant field or do not claim technologies that would be pursued through the FDA approval process by pharmaceutical companies.

178. There were other categories on which I kept records but which are not germane to the question of FDA approval for pharmaceuticals. For instance, there is another sizable cluster of patents granted to products which are intended to function more like food or probiotics, which do not require FDA approval, than like pharmaceutical products. Many of these patents have been assigned to Nestec S.A., a subsidiary of Nestle. *See, e.g.*, U.S. Patent No. 8,318,150 (issued Nov. 27, 2012) (claiming "[a] method for weight loss in a mammal comprising the step of administering a composition comprising an effective amount of *Lactobacillus rhamnosus* CNCM I-4096 to a mammal in need of weight loss "). I also maintained a list of patents claiming inventions in the medical device or diagnostic field. *See, e.g.*, U.S. Patent No. 9,670,550 (issued June 6, 2017) (claiming "[a] method for screening whether a test subject has a liver cancer and/or an increased risk of liver cancer, comprising: assaying gut microbiota . . . and determining whether a ratio of Gram-positive bacteria to Gram-negative bacteria in the assayed sample collected from the test subject exceeds a range of ratios").

179. Interestingly, there are a small number of patents that fit this description. For instance, U.S. Patent No. 7,713,726 claims "[a] composition comprising an isolated *Bacillus coagulans* GBI-30 strain." U.S. Patent No. 7,713,726 (issued May 11, 2010). However, these patents were issued before the Supreme Court's recent interest in § 101 cases, and I am skeptical that their validity would hold up if challenged in court.

Bacteroides, and a plurality of viable non-pathogenic or attenuated pathogenic *Escherichia coli*." Instead, the patent claims this mixture in "[a]n oral pharmaceutical composition in a capsule or microcapsule adapted for enteric delivery."[180] These additions limit the scope of the claims so that not all mixtures of the identified microbiota will fall within its scope.

Many other claims are drawn to look even more like standard formulation claims.[181] For instance, U.S. Patent No. 9,585,921 claims a composition "comprising a purified population of *Acetivibrio ethanolgignens* spores," but only when that composition "is derived from fecal material subjected to ethanol treatment or heat treatment."[182] This additional step not only takes the microbiota in question out of the "product of nature" category, but it also narrows the scope of the claims.

More interestingly, more than twenty patents have been granted that cover genetically engineered strains of bacteria, either in isolation or in combination with other strains.[183] This is not surprising, given the Supreme Court's explicit holding in *Diamond v. Chakrabarty* that genetic engineering of this type would distinguish such a claim from those at issue in *Funk Brothers*.[184] More recently, *Myriad* also made clear that claims like these should have no problem passing through the § 101 filter.[185] The logic here is simple: the products these patents claim are not found in nature. They were made in a lab, like the genetically engineered bacterium in *Chakrabarty* or the cDNA fragments in *Myriad*.[186]

Finally, a few patents include standard pharmaceutical composition of matter claims but are drawn to small-molecule byproducts of microbiota activity, to small molecules that are believed to modulate the effect of the mi-

180. U.S. Patent No. 9,682,108 (issued June 20, 2017).

181. *See, e.g.*, U.S. Patent No. 9,308,226 (issued April 12, 2016) (claiming "[a]n oxygen-free or substantially oxygen-free pharmaceutical preparation, comprising: (a) a formulation comprising: (i) a frozen, freeze-dried, spray-dried, lyophilized or powdered entire or at least 90% anaerobic microorganism population of a complete microbiota of a fecal sample; or (ii) all or at least 90% anaerobic microorganism population of a complete microbiota of a fecal sample in an excipient, a saline, a buffer, a buffering agent or medium, or a fluid-glucose-cellobiose agar (RGCA) medium, (b) an oxygen scavenging material, and (c) an air tight or an anaerobic container, wherein the pharmaceutical preparation provides an at least about 99.5% oxygen-free or oxygen-free containment or storage of the anaerobic microorganism population of (a)(i) or (a)(ii) in the air tight or the anaerobic container").

182. U.S. Patent No. 9,585,921 (issued Mar. 7, 2017).

183. *See, e.g.*, U.S. Patent No. 9,845,342 (issued Dec. 19, 2017); U.S. Patent No. 9,688,967 (issued June 27, 2017); U.S. Patent No. 9,593,339 (issued Mar. 14, 2017); U.S. Patent No. 9,453,232 (issued Sept. 27, 2016); U.S. Patent No. 9,040,302 (issued May 26, 2015) (claiming a *Streptococcus thermophilus* bacterium genetically modified to have particular characteristics); U.S. Patent No. 8,986,675 (issued Mar. 24, 2015).

184. 447 U.S. 303, 309–10 (1980).

185. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 594–95 (2013).

186. *Chakrabarty*, 447 U.S. at 310; *Myriad*, 569 U.S. at 594–95.

crobiome,[187] to small molecules in combination with microbiota,[188] or to standard biologic drugs such as antibodies.[189] These claims allow inventors to surmount the § 101 doctrinal barriers I identify above and obtain patent portfolios that more closely resemble traditional pharmaceutical patents.

The majority of relevant patents (175) claim methods for using particular microbiota to treat disease. Some of these claims are quite general, targeted at the treatment of "gastrointestinal symptom[s],"[190] but others are quite specific, targeted at hepatic encephalopathy,[191] ulcerative colitis,[192] *C. difficile* infections,[193] or autism.[194] Many of these method claims specify the composition of microbiota within the claims in a way that suggests the inventors are seeking to use a method claim to cover all uses of the relevant composition of microbiota.[195]

For instance, one company in this space is the assignee on several patents adopting the following form:

> A method of treating an occurrence or a recurrence of a *Clostridium difficile* infection, comprising administering to a human subject in need thereof an effective amount of a therapeutic composition comprising a first purified bacterial population consisting of a first bacteria comprising a 16S rDNA sequence at least about 97% identical to a 16S rDNA sequence present in a reference *Collinsella aerofaciens* OTU, and a second purified bacterial population consisting of a second bacteria comprising a 16S rDNA sequence at least about 97% identical to a 16S rDNA sequence present in a reference bacterium of the family Clostridiaceae listed in Table 1, wherein a synergistic combination of the first bacteria and the second bacteria is cytotoxic or cytostatic to a *Clostridium difficile*.[196]

These claims avoid the § 101 problem posed by the compound claims, because they go beyond claims to products of nature by requiring action steps (here, "administering to a human subject" the therapy). However, they are possibly subject to the detection and enforcement problems articulated above.[197]

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187. *See, e.g.*, U.S. Patent No. 9,539,281 (issued Jan. 10, 2017) (claiming an isolated lipidated polysaccharide A isolated from *Bacteroides fragilis*).

188. *See, e.g.*, U.S. Patent No. 9,492,488 (issued Nov. 15, 2016) (claiming a combination of an antibiotic and a particular probiotic formulation).

189. *See, e.g.*, U.S. Patent No. 9,815,889 (issued Nov. 14, 2017).

190. U.S. Patent No. 9,572,841 (issued Feb. 21, 2017).

191. U.S. Patent No. 9,694,039 (issued July 4, 2017).

192. U.S. Patent No. 9,642,880 (issued May 9, 2017).

193. U.S. Patent No. 9,669,059 (issued June 6, 2017).

194. U.S. Patent No. 9,320,763 (issued Apr. 26, 2016).

195. This is a common strategy. *See, e.g.*, Univ. of Rochester v. G.D. Searle & Co., 375 F.3d 1303 (Fed. Cir. 2004).

196. U.S. Patent No. 9,533,014 (issued Jan. 3, 2017).

197. *See supra* Section III.C.

Some scholars would argue that the seeming paucity of patent protection in this area is a problem to be solved, perhaps by lobbying Congress.[198] Much of microbiome science is still at the fecal-transplant stage, and scientists do not yet have a strong enough appreciation of which genes (if any) are most important for the functioning of particular microorganisms in our guts, so that those genes may be genetically engineered and patented. To put it another way, they would argue that stool is a bridge technology. No scientist or physician hopes that stool transplants will still be the norm even a decade from now. The hope is that soon we will be harnessing engineered strains, metabolites, or other technologies to fight and prevent disease. But if a lack of patent protection in the current generation dissuades investors from developing current therapies that do not rely on genetic engineering, it may be difficult to develop the next generation of therapies, for which patents would be available.

I am not so certain. To be sure, companies involved in the microbiome space may be disadvantaged relative to pharmaceutical companies operating in related but distinct areas. And if this disadvantage is not justified by the potential medical and financial returns, that may be a problem for both innovation and social welfare. But from a more absolute perspective, it is difficult to conclude without additional evidence that the absence of traditional patent protection is itself a problem. Dozens of companies, both small and large, are developing drugs in this space, and the scientific community as a whole could hardly be more excited. Although there may be *more* companies if patents were more easily available, it is difficult to say that there is not *enough* investment here to produce a host of new, innovative products.[199] This is largely because companies are employing other mechanisms to protect their investments, and I turn now to consideration of those mechanisms.

IV. Alternative Approaches to Microbiome Innovation

Taken together, patent-law doctrine and an examination of granted patents suggest that companies are finding it difficult to obtain and enforce patents on microbiome-related technologies, especially as compared to the relative availability of such patents in more traditional areas of the pharmaceutical sector. But is this descriptively accurate, and do scientists and IP counsel perceive that to be the case? If so, what additional mechanisms (if any) are being used to protect the key investments made into these new technologies? Are universities and small companies able to execute deals with other companies in the absence of patent protection? More worry-

198. *Cf.* Christopher M. Holman, Mayo, Myriad*, and the Future of Innovation in Molecular Diagnostics and Personalized Medicine*, 15 N.C. J.L. & Tech. 639, 673–77 (2014) (arguing that "an aggressive application of *Mayo* . . . could severely impact the availability of effective patent protection for future innovations in molecular diagnostic testing and personalized medicine").

199. This is separate from the question of whether the level of investment we observe is socially optimal, a question I do not attempt to answer here.

ingly, are scientists and companies making decisions about which technologies to pursue based on the availability of traditional intellectual-property protection? The burgeoning field of microbiome research provides a case study through which to examine some of the propositions that are so central to modern patent scholarship. This Part bolsters the analysis from Parts II and III, contextualizing those findings through a series of structured interviews I conducted with key stakeholders.

A. *Industry Survey*

It is difficult to obtain a full picture of the microbiome-research landscape using only publicly available sources. Some pieces of information—about how different actors in the field view particular innovation incentives, how they evaluate competing investment opportunities, and the like—can only be answered by asking actors in the field directly about their experiences with these issues. So I conducted a series of semi-structured interviews with twelve key stakeholders[200]: scientific researchers both in academia and in companies, executives at these companies, technology-transfer officials in academia, and intellectual-property counsel for companies moving forward with these technologies.[201]

These stakeholders were identified in multiple ways. First, I included individuals or companies who had applied for or received one of the patents examined in Part III. Second, I searched a number of widely read industry websites and databases[202] for companies and lawyers working in the field. Third, using the previous two methods and a general Google search, I identified universities with particularly robust microbiome-research programs (to include their technology transfer offices in the sample). Fourth, I implemented snowball sampling[203] by asking colleagues in the field and interview subjects if they knew anyone else who might be able to provide me with a useful perspective.

Importantly, I excluded companies who did not appear to be developing technologies that would require FDA approval. For instance, a number of companies, including global conglomerates like Nestle, seem to be interested

200. These interviews were under Wash. Univ. St. Louis Institutional Review Board (IRB) oversight (reference number 201703111).

201. Many of the stakeholders I spoke with had experience in a number of these roles. Five had worked as attorneys (three external and two in-house), two as technology-transfer officers at different universities, three as scientists, three as industry executives at different companies, and two as industry consultants more generally.

202. Including Endpoints News, *see* ENDPOINTS NEWS, https://endpts.com/ [https://perma.cc/JTM5-7BZK], FierceBiotech, *see* FIERCEBIOTECH, www.fiercebiotech.com [https://perma.cc/9YDV-495A], and ClinicalTrials.gov, *see* U.S. Nat'l Library of Med., CLINICALTRIALS.GOV, https://clinicaltrials.gov [https://perma.cc/J8AZ-8K3G].

203. Snowball sampling is a tool by which researchers use current subjects to identify and contact additional potential subjects.

in developing food products that manipulate the eater's microbiome.[204] In theory, it is possible that these companies might be interested in making the kinds of health claims that would require full FDA approval as a drug. However, based on their existing product portfolios, I deemed it unlikely that they would do so. It is more likely that the company would seek regulation as a traditional food or, at most, as a "medical food" requiring far less regulation than a typical pharmaceutical product.[205]

My starting sample is likely to be representative of the field of microbiome research as a whole. Because the set of companies in this space is both small and finite, it is likely that the combination of publicly available research to identify relevant actors plus the use of snowball sampling means that I identified essentially all the important actors in the field. If anything, by using existing patents as a source of information, it is likely that I have oversampled companies who place value on patents, whether obtained and asserted or not. Therefore, I have confidence that the views expressed by the participants have not underestimated the importance of patents within the microbiome-research field.

My sample here may be skewed in one relevant sense: I only consider companies that currently exist. If a company either has not begun promising research or folded due to lack of funding, that company is unlikely to show up in my sample. If the company's lack of funding is due to its lack of patent protection, that would be a potential bias in my results. At the same time, it is relatively early in the field of microbiome research, and it would be surprising if company closures of this type were a widespread phenomenon thus far. Further, it is surely the case that companies fail to obtain funding and fold in other areas of the pharmaceutical industry as well.

But because most invitees did not respond and I was able to interview only twelve individuals, it is important to take care when drawing larger conclusions from these efforts. To be sure, the universe of companies and researchers operating in this space is fairly small, especially compared with more established fields of research like cancer or heart disease. But it is difficult to be certain that comments I recorded from a single scientist or company would be truly representative in a larger pool of potential responders. As such, some of these comments may be best understood as providing context within a developing field and supporting questions for further research. I leave the question of the interviews' generalizability to the broader pharmaceutical industry for Part V.

B. *Interview Results*

In short, most of my interviewees supported the descriptive account of the availability of patent protection in the microbiome space as presented *supra* in Part III. Many companies report possessing thin if any patent pro-

204. *See supra* note 178 for relevant examples.

205. *See* 21 U.S.C. § 360ee (b)(3) (2012).

tection for the products they are developing, and technology-transfer offices are in some cases declining to apply for patent protection altogether. Even those patents that exist are not commonly asserted, or at least not asserted in publicly available legal filings. Further, other companies that are developing potentially competing products do not report receiving demand letters from companies with relevant patents.[206]

First, lawyers and other IP professionals largely concurred in my assessment of the difficulty of patenting many of these technologies, with one technology-transfer professional noting that "so much of the basic science and even the translational research that's happened in microbiome studies has focused on what, essentially, the PTO and Supreme Court have decided are natural products," which in their view "makes it very challenging, sort of, given the restrictions that the law has placed on getting patent protection of that specific category of compositions."[207] Another interviewee, a lawyer, specifically noted that "the case that keeps killing us in this field is *Funk Brothers* . . . [i]t doesn't help us that the first real patentable subject matter case was directed toward this kind of technology."[208] They also commented that "[a] formulation ends up being one of the core patents sometimes," recognizing the difficulty in patenting the organisms involved here.[209]

Lawyers also offered nuance to the enablement and written-description concerns I identified above. One external counsel emphasized the use of deposits.[210] Another suggested that, in their view, "[w]hen the examiners are starting to apply [§] 101, they don't often do a clean analysis and almost raise [§] 102, [§] 103, and [§] 112 issues with their [§] 101 analysis."[211] This individual saw § 112 issues being expressed more commonly as part of the § 101 inquiry,[212] consistent with the view of scholars who have noted the close connections between these doctrines.[213]

Interestingly, although intellectual-property lawyers and technology-transfer officials might *prefer* to obtain patents in this space, they report being untroubled by their inability to obtain the kinds of primary-product patents that might be most valuable to their institutions and clients.[214] As one such interviewee told me, "patent protection isn't an end-all, be-all the way it

206. To be sure, it is still early in the development of the field—it may be that once products are approved and marketed (and therefore once damages are more readily available), this will change. Interview with Lawyer B (Aug. 2017) (on file with author); Interview with Scientist B (Aug. 2017) (on file with author).

207. Interview with Technology Transfer Officer A (July 2017) (on file with author).

208. Interview with Lawyer A (Aug. 2017) (on file with author).

209. *Id.*

210. *Id.*

211. Interview with Lawyer B, *supra* note 206.

212. *Id.*

213. *See, e.g.*, Eisenberg, *supra* note 155, at 267; Paul R. Gugliuzza, *Quick Decisions in Patent Cases*, 106 GEO. L.J. 619, 654 (2018).

214. Interview with Lawyer A, *supra* note 208.

has traditionally been in pharmaceuticals in terms of just really carving out a space that others really can't touch."[215] Another lawyer noted that "if the science is good . . . we'll figure out the IP story."[216] However, scientists are more likely to express concern about the fact that their institutions (academic or corporate) are not obtaining typical patent protections over their inventions.

These scientists report different motivations for their concern. Some fear that other projects (which are traditionally susceptible to patenting) will be prioritized over theirs.[217] Others fear that the technology will not be developed further (either by their company or by a corporate partner, in the case of academic scientists) in the absence of patent protection.[218] Unfortunately, due to the small number of interviews, it is difficult to say whether one particular concern is dominant over all others or even broadly prevalent.

But this relative lack of patent protection as compared to other segments of the pharmaceutical industry does not appear to be stifling development of new technologies. Instead, companies and universities are increasingly turning to other types of protection for their innovations. As one technology transfer professional told me, "the scope of an individual patent tends to be much narrower now, and so patent protection is only one strategy that people use."[219] Companies are using two main policy levers—trade secrecy and FDA exclusivity periods—both of which are well-studied in the literature.[220]

In the period of time before FDA approval (and here it is important to note that no company has yet obtained FDA approval for a microbiome-based therapy, although multiple companies are well into the clinical-trial process[221]), companies are chiefly relying on trade secrecy to protect their manufacturing processes, clinical-trial data, and information about their donors.[222]

Companies are also looking ahead to the prospect of FDA-administered exclusivity periods post-approval.[223] On this subject, one lawyer even told me that he thinks of himself "as an exclusivity attorney and not a patent attorney because your client overall wants to know about how to achieve the best exclusivity position, whether it's via patents, or regulatory [exclusivi-

215. Interview with Industry Consultant A (July 2017) (on file with author).

216. Interview with Lawyer C (Sept. 2017) (on file with author).

217. Interview with Scientist A (July 2017) (on file with author).

218. Interview with Scientist C (Aug. 2017) (on file with author).

219. Interview with Technology Transfer Officer A, *supra* note 207.

220. *See, e.g.*, Heled, *supra* note 8; Price & Rai, *supra* note 63.

221. *See, e.g.*, *Seres Therapeutics Initiates SER-109 Phase 3 Study in Patients with Multiply Recurrent* C. difficile *Infection*, BusinessWire (June 12, 2017, 7:07 AM), http://www.businesswire.com/news/home/20170612005312/en/Seres-Therapeutics-Initiates-SER-109-Phase-3-Study [https://perma.cc/MXY8-AB4C].

222. Interview with Technology Transfer Officer B (Apr. 2017) (on file with author); Interview with Lawyer C, *supra* note 216.

223. Interview with Lawyer C, *supra* note 216 ("[I]n the worst case in the US you'll get 12 years of data protection.").

ties], or a combination of both."[224] As noted above, at least three companies have already received orphan designations for their microbiome-related products,[225] and, if approved, those companies will receive seven years of market exclusivity for their therapies. In other words, during that seven-year period the FDA may not approve a new or generic drug application for the same product and indication.[226] Companies are also looking ahead to the twelve-plus years of data exclusivity available for biologic drugs (a category that includes the microbe-based products under development by the companies in this space).[227] Although data exclusivity is technically more limited than market exclusivity, functionally, for FDA purposes, data and market exclusivity are often interchangeable.

In conducting this survey, I also wondered whether academics would feel more free to conduct research in this area due to the lack of patent protection. On the whole, academic scientists seemed to be unconcerned about either the presence or lack of patents in this area. That is, it did not seem that scientists were or had been worried about an anticommons problem.[228] They felt free to conduct the research projects of their choice, and none of the scientists I spoke with had received cease-and-desist letters or other communications from patent owners, let alone been the subject of a patent-infringement action. This finding may be consistent with recent empirical research suggesting that even where patents exist, they are often ignored by academic researchers.[229]

Another potential concern regarding the lack of patents in this space, as described above, is the role patents play in enabling the transaction of valuable information between parties.[230] It might be that the relative lack of patents in this space makes it difficult for small companies to obtain funding from venture capitalists, either because those funders look for traditional patent protection in the pharmaceutical space or because the small companies

224. Interview with Lawyer B, *supra* note 206.

225. *Orphan Drug Designation for "Fecal Microbiota" Granted to Rebiotix*, *supra* note 121 (granted Mar. 10, 2014); *Orphan Drug Designation for "Encapsulated Spores from Fecal Microbiota" Granted to Seres*, *supra* note 121 (granted Aug. 19, 2015); *Orphan Drug Designation for "Alloegeneic Fecal Microbiota" Granted to MaaT Pharma*, *supra* note 121 (granted Feb. 28, 2018).

226. 21 U.S.C. § 360cc(a) (2012) (Orphan Drug Act, conferring seven years of market exclusivity).

227. 42 U.S.C. § 262(k)(7)(A) (2012) (Biologics Price Competition and Innovation Act, conferring twelve years of data exclusivity); Sachs & Edelstein, *supra* note 116, at 398. Importantly, companies may receive more than one exclusivity period. In the event that a company receives approval for an orphan biologic product, they are entitled to both the Orphan Drug Act's seven-year market exclusivity period as well as the twelve-year biologic data exclusivity period, which will run concurrently.

228. *See generally* Heller & Eisenberg, *supra* note 23.

229. Lisa Larrimore Ouellette, *Who Reads Patents?*, 35 Nature Biotechnology 421 (2017).

230. *See supra* text accompanying notes 37–44.

fear disclosing information to funders in meetings without the security of patent protection. It might also be that the lack of patents makes transactions between universities and small companies, or small companies and large companies, more difficult for similar reasons.

This fear also does not seem to be borne out. Although it is never *easy* to obtain venture-capital funding, essentially all the small companies in this field have publicly disclosed funding arrangements with a number of diverse partners, and several have completed multiple rounds of venture funding. Further, a number of smaller companies have executed highly publicized deals of various types with large pharmaceutical companies.[231] And when I spoke with interviewees who advise venture capitalists on these deals, they commented that although many venture capitalists do want to see a patent portfolio, they recognize the difficulties in patenting these particular technologies and want to see "that the portfolio is well thought out, and that they're thinking about this portfolio in view of the changing landscape."[232] Recent empirical work, which finds that orphan-drug designations themselves are signals for potential investors, supports this statement more broadly.[233] A technology-transfer officer noted that a number of companies in this field "have been founded more directly by scientists," under a "start-up model where university researchers are able to spin out their ideas into companies."[234] Under these circumstances, patents may be less critical if there is personnel continuity.

It is critical to emphasize the "but-for" story here as a potential limitation on my conclusions. I have demonstrated that there are many companies developing products in the microbiome space with thin if any patent protection and that there have been some number of deals executed between companies without the standard intellectual-property backing. But I have not demonstrated that patents play *no* role in the development of these technologies. It may be that in the presence of more robust patents, there would be more companies developing products, and we would observe more deals being executed, or we would observe different types of corporate structures forming. A number of industry participants of course asserted that they would like greater access to patent protection for these technologies, but it is, as usual, impossible to assess what the but-for world would look like in such a case.

There is one way in which the but-for world may be manifested in the current sample. It may be that scientists and companies make decisions about which technologies to move forward through the development process based on the availability of traditional intellectual-property protection. For

231. *See supra* text accompanying notes 110–112.

232. Interview with Lawyer B, *supra* note 206.

233. Philippe Gorry & Diego Useche, *Orphan Drug Designations as Valuable Intangible Assets for IPO Investors in Pharma-Biotech Companies*, (Nat'l Bureau of Econ. Research, Working Paper No. 24021, 2017), http://www.nber.org/papers/w24021 [https://perma.cc/JC47-WVWL].

234. Interview with Technology Transfer Officer A, *supra* note 207.

instance, one interviewee suggested that companies may choose to develop microbiome-based therapies that take advantage of the use of small molecules and their ability to manipulate the microbiome, because those small molecules—or at the very least their use in the microbiome context—can be patented traditionally.[235]

If true, this would be concerning, because it would suggest that companies are choosing which therapies to develop not based solely on the science or potential social-welfare gains, but on their ability to protect more effectively their investment in the field. This observation, however, would also be in keeping with prior scholarly work in the field. As Professors Amy Kapczynski and Talha Syed have argued, the availability of patent protection will "predictably and systematically distort private investment decisions . . . by overstating the value of highly excludable information goods and understating the value of highly nonexcludable ones."[236] Researchers are dissuaded from studying new uses for old drugs or examining negative information about existing drugs because those findings are comparatively nonexcludable.[237]

I did not find widespread evidence for that version of theory, in the sense that no company scientist I spoke with openly admitted to engaging in this behavior. But because I spoke with only a few scientists, it is difficult to be fully confident in these responses. Other pieces of suggestive evidence point in either direction. As I mentioned above, some scientists expressed concern that their firms would choose to proceed (or provide an advantage to in some other way) with more traditional therapies susceptible to patent protection, over their projects. If a scientist felt this concern particularly strongly (even if it were an imagined threat), she might choose to proceed with a microbiome-based project that is amenable to traditional patenting. At the same time, however, many lawyers and company executives worked to reassure these scientists that their projects would be adequately supported. To the degree that this support is believed and accepted, scientists may proceed with their research with confidence.

I did, however, find evidence to support a different version of this concern. Namely, a number of interviewees expressed a desire to minimize their regulatory burden or advised clients to minimize their regulatory burden, which in at least some cases resulted in companies choosing to pursue product-development pathways that would not require FDA approval.[238] In other words, rather than making health claims about a particular technology, a company might choose to develop a probiotic or other product that can be developed with much less regulatory scrutiny. As one interviewee put it, "let's say you have a good microbiome solution. Is the prescription route the

235. Interview with Lawyer A, *supra* note 208.

236. Kapczynski & Syed, *supra* note 19, at 1907.

237. *Id.* at 1926.

238. Interview with Lawyer A, *supra* note 208.

way to go? What about all these commercials with Activia and all these other things? Those are putting particular types of bugs that are pretty easy to get a hold of and you sell it for—a yogurt for $19, or whatever it may be. How can that compete with a $500 million plus clinical effort?"[239]

From the perspective of wanting to encourage the development of evidence about how the microbiome can be manipulated to help treat or cure disease, these comments may be somewhat concerning. If the FDA approval pathway combined with the absence of patent protection is causing companies to pursue less onerous regulatory pathways, and therefore to produce less scientific evidence, it may be that a patent-based intervention would be warranted. However, it is difficult to disentangle the effects of the lack of patent protection and the onerous FDA approval process. Further, it is likely that some behavior like this happens at present.[240] Therefore, it is difficult to be sure whether the patent dynamics in the microbiome field have led to an *increase* in this activity.

To the extent these results are representative of this sector of the industry as a whole, we might conclude that the field of microbiome research is succeeding—thriving, even—in the absence of real patent protection. What might this success so far tell us about the pharmaceutical industry more broadly and its relationship to the patent system? I take up that question in the next Part.

V. Rethinking the Conventional Wisdom

This case study on the microbiome presents a challenge to the conventional wisdom that if any technological sector truly requires patents for the development of new products, it is pharmaceuticals. For scholars and policymakers who point to the pharmaceutical industry as the primary justification for the patent system, this case study shows that patents may be useful, valuable, and even important to the development of new microbiome-based products, but they are not *necessary* for the development and commercialization of these new pharmaceuticals. To the extent that this conventional story about the pharmaceutical industry has pervaded the policy discourse, perhaps many of those discussions should now be revisited. This Part first considers the extent to which this case study ought to cause us to rethink the conventional wisdom, and it then goes on to consider policy implications for these findings.

239. Interview with Lawyer C, *supra* note 216.

240. *See, e.g.*, Victor Fleischer, *Regulatory Arbitrage*, 89 Tex. L. Rev. 227, 230 (2010); Rachel E. Sachs, *Mobile Health Innovation and Interagency Collaboration*, Annals of Health L., Summer 2017, at 1, 9; Nicolas P. Terry, *Regulatory Disruption and Arbitrage in Health-Care Data Protection*, 17 Yale J. Health Pol'y L. & Ethics 143, 146 (2017).

A. *Revising the Paradigm for Pharmaceutical Innovation*

Facially, the results above challenge the account of the pharmaceutical industry as "the golden child" of the patent system.[241] It is important, however, to assess how broadly these findings may be generalized. To the extent they apply beyond the particular microbiome context, there are two larger categories to which these findings may apply: small-molecule drugs and biologics.[242] Small-molecule drugs like aspirin, which can be made through standard chemical synthesis in a laboratory, had historically dominated the pharmaceutical market. More recently, pharmaceutical companies have developed expertise in the creation of biologics, larger molecules made in living cells.[243] As Professors Nicholson Price and Arti Rai have written memorably, "[i]n terms of size and rough complexity, if an aspirin were a bicycle, a small biologic would be a Toyota Prius, and a large biologic would be an F-16 fighter jet."[244]

Small-molecule drugs are not only comparatively easier to make than are biologics. They are also largely self-disclosing. Once a rival company knows what the relevant compound is (a fact that is publicly available at the time of FDA approval, if not before), they can fairly easily reproduce the drug using well-known analytic methods.[245] This ease of imitation is one reason patents have long been held out as vital in the pharmaceutical space. If generic companies can bring a small-molecule drug to market for just a few million dollars,[246] pharmaceutical companies may be rightly concerned about the potential for generic firms to free-ride off their investment in research and development. More vividly, the term "patent cliff" applies clearly in the context of small-molecule drugs.[247] Immediately after patent expira-

241. Roin, *Unpatentable Drugs*, *supra* note 34, at 507.

242. At present, pharmaceutical technologies fit into one of these two categories. There are variations on how strongly some of the characteristics of the two categories fit—for instance, vaccines are regulated as biologic products but are often not as hard to reverse engineer as some of the new biologic drugs.

243. Ajay Gautam & Xiaogang Pan, *The Changing Model of Big Pharma: Impact of Key Trends*, 21 Drug Discovery Today 379, 379 (2016).

244. Price & Rai, *supra* note 63, at 1026 (citing Deepak Gupta et al., *A CMO Perspective on Quality Challenges for Biopharmaceuticals*, BioProcess Int'l (Oct. 1, 2013, 9:00 AM), http://www.bioprocessintl.com/manufacturing/antibody-non-antibody/a-cmo-perspective-on-quality-challenges-for-biopharmaceuticals-347335/ [https://perma.cc/HDC2-G4SM]).

245. *Id.* at 1036.

246. Henry Grabowski et al., *Does Generic Entry Always Increase Consumer Welfare?*, 67 Food & Drug L.J. 373, 390 (2012) (estimating the approval costs of small-molecule generic drugs at $2 million).

247. *See, e.g.*, Michael A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 Am. U. L. Rev. 305, 321, 339–40 (2016).

tion,[248] generic firms may enter and drive down prices significantly, up to 80% off the branded price with the entry of multiple generics.[249]

Biologics, by contrast, are not self-disclosing in this way. Professors Price and Rai have explained how knowing the identity of a particular biologic is not sufficient to enable other companies to make biosimilar versions of the product.[250] As a result, biologics can be protected highly effectively using trade secrets.[251] Indeed, the very reason the product is called a *biosimilar* is that it cannot (at present) be shown to be bioequivalent in the way that small-molecule drugs can be. Experts have suggested that it may cost a few hundred million dollars to bring a new biosimilar to market, and that savings on the order of only 20–30% can be expected as a result.[252]

It may be that the results presented in the previous Part are generalizable to biologics, but not to the small-molecule context. Like biologics, many (though not all) new microbiome technologies are not completely self-disclosing. The existence of the enablement problem as described in Section III.B is one supporting example. Telling a potential competitor the particular strains of microbes that are involved in a microbiome-based technology is typically not sufficient to tell the competitor how to make that technology.[253] There are often significant differences in how particular microbes behave that depend on their development process and their manufacturing process, much like biologics. It may be, therefore, that my analysis extends more broadly to all or at least some biologics, which can be protected effectively using trade secrets, but does not extend to the category of self-disclosing, small-molecule drugs.

Extending my analysis to biologics but not small-molecule drugs may not entail a wholesale rejection of the conventional wisdom, merely a narrower application of it. Many scholars expressing this typical view of the relationship between patents and the pharmaceutical industry expressly tie their observation to both the high costs of development *and* the ease of imitation involved.[254] To the extent that only small-molecule drugs can be easily imitated, it may be that the conventional wisdom is accurate, but that (at least for now) it is limited to the context of small-molecule drugs. The conventional wisdom developed at a time when small-molecule drugs dominated both pharmaceutical-industry pipelines and medical practice, and for that reason it may have been sufficient shorthand under those conditions.

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248. Assuming the patent expires after the expiration of all relevant exclusivity periods, of course.

249. CVS Health, *Basics About Biosimilars: The Savings Potential and the Challenges*, Insights Executive Briefing, no. 6, 2016, http://investors.cvshealth.com/~/media/Files/C/CVS-IR-v3/reports/biosimilars-prospect-050316.pdf [https://perma.cc/27YM-5CJB].

250. Price & Rai, *supra* note 63, at 1032–37.

251. *Id.* at 1046–47.

252. CVS Health, *supra* note 249, at 2.

253. *See supra* text accompanying notes 160–169.

254. *See, e.g.*, Eisenberg, *supra* note 34, at 721; Roin, *Unpatentable Drugs*, *supra* note 34, at 508.

However, things have changed. Drug companies are investing more and more in biologics, rather than small-molecule drugs.[255] These drugs are increasingly profitable—in 2016, six of the top eight drugs in the United States by revenue were biologics.[256] To be sure, companies are still investing in and producing new small-molecule drugs, with the innovative Hepatitis C drugs being a recent example.[257] But scholars can no longer give primacy to a view of innovation policy developed in the context of a different pharmaceutical paradigm. Patents may have been critical for the development of small-molecule drugs. But patents may not in fact be necessary for some of the newest, most innovative products on the market. Scholars must be precise about the role that patents play in the context of these new pharmaceutical technologies. And policymakers ought to resist calls for modifying the patent system to more clearly enable these technologies to obtain patent protection. Congress does not obviously need to override *Funk Brothers*, or limit the reach of § 112, or take steps to increase the length of patent protection for drugs that are slower to market.[258] This is not a problem to be solved by increasing patent protection, and it may not be a problem at all.

Scholars should also reconsider the role that patents play in the context of the overall ecosystem of innovation incentives for pharmaceuticals. Over the past three decades, policymakers have built an entire edifice of innovation incentives around pharmaceuticals specifically.[259] As examined in Section I.B, the government provides federal funding on the front end, tax credits during the R&D process, exclusivity periods post-approval, trade secrets throughout, and additional benefits for particular types of pharmaceutical interventions.[260] These incentives do not perfectly replicate the function of the patent system,[261] and patents are one of the few incentives to operate in the period before products come to market. However, trade secrecy in particular may prove to be a sufficient substitute for patents during this period

255. *See, e.g.*, Ralf Otto et al., *Rapid Growth in Biopharma: Challenges and Opportunities*, McKinsey & Co. (Dec. 2014), https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/rapid-growth-in-biopharma [https://perma.cc/4DRL-9PCH].

256. Nigel Walker, *Biologics: Driving Force in Pharma*, Pharma's Almanac (June 5, 2017, 12:31 PM), https://www.pharmasalmanac.com/articles/biologics-driving-force-in-pharma [https://perma.cc/3K6F-CAF7].

257. *See* Ted Alcorn, *Hepatitis C Drugs Save Lives, but Sick Prisoners Aren't Getting Them*, N.Y. Times (Mar. 15, 2018), https://www.nytimes.com/2018/03/15/us/hepatitis-c-drugs-prisons.html (on file with the *Michigan Law Review*).

258. *See, e.g.*, Roin, *supra* note 2.

259. Most notably, since the passage of the Orphan Drug Act in 1983, see 21 U.S.C. § 355(j)(5)(F)(ii) (2012), and the Bayh-Dole Act in 1984, see 21 U.S.C. § 360cc(a) (2012).

260. Price & Rai, *supra* note 63, at 1026–29.

261. *See id.*

of time. Ultimately, we should not be astonished that the removal of a single one of these incentives does not destroy the entire system.[262]

B. *Implications for Policy and Scholarship*

Revising our appreciation of the conventional wisdom around the centrality of patents to pharmaceutical innovation has implications for both policy and scholarship. Most importantly, scholars and policymakers ought to consider the pros and cons of the weakening of patent incentives in the microbiome context. There are at least three potential implications to consider. First, it may be that companies' inability to obtain standard patent portfolios is causing them to increase their reliance on other innovation incentives in ways that may be socially harmful. Chiefly, companies appear to be opting to keep at least some information as a trade secret rather than attempting to protect it through the patent system.[263] Using trade secrecy rather than patents deprives the public of disclosure that may help move the field forward scientifically, even if the particular treatments cannot be copied in the short-term. Further, trade secrets are not limited temporally the way that patents are, and as such they can help companies maintain their monopolies beyond the twelve-year period of exclusivity.

Second, the results above provide a policy argument in favor of the current twelve-year exclusivity period for biologic drugs. To the extent that patents are less readily available for these technologies and that twelve years is roughly the average patent term remaining after FDA approval,[264] a twelve-year exclusivity period provides companies with essentially the same post-approval protection they would otherwise be entitled to by law. I and others have previously expressed concern over the length of the exclusivity period, but to the extent that it is a *replacement for* rather than a *supplement to* the patent system, the period may be more defensible than previously recognized.[265]

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262. *Cf.* Mark A. Lemley, *The Surprising Resilience of the Patent System*, 95 Tex. L. Rev. 1, 2 (2016) (explaining how patent owners fear that underprotection from the patent system "might leave innovators without adequate protection").

263. It is unlikely that companies are using other innovation incentives as substitutes. Companies usually opt for *both* patents and FDA exclusivity periods, and nothing about weakening patent incentives in this case suggests that the monopolistic effects of those exclusivity periods will express themselves in more problematic ways.

264. Eisenberg, *supra* note 74, at 352; Hemphill & Sampat, *supra* note 84, at 330.

265. *See* U.S. Fed. Trade Comm'n, Emerging Health Care Issues: Follow-on Biologic Drug Competition vi (2009), https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf [https://perma.cc/8U7G-TP4G] ("[T]here is very little data to suggest that biologic drugs under development are likely to be unpatentable."). To the extent that recent case law may result in a narrowing of patent protection for some biologics, see Amgen Inc. v. Sanofi, 872 F.3d 1367, 1375 (Fed. Cir. 2017), this argument may grow in importance.

Third, and finally, the lack of patent protection for microbiome-related therapies at the present time can be viewed as an opportunity to encourage the progress of innovation without traditional intellectual property. The scholarly literature in this field has grown tremendously over the past few years,[266] with scholars taking a broad view of potential legal solutions to innovation problems. Many scholars have explored ways in which community norms (rather than other legal levers) may function as an alternative to patent or copyright law.[267] Other scholars have considered the potential of alternative legal mechanisms, such as prizes or government grants, to incentivize innovation, including presenting case studies of the role of alternative innovation mechanisms in particular industries.[268]

However, thus far the literature has focused more closely on industries in which the costs to develop an innovation are relatively low, as compared with the high costs of developing a new pharmaceutical product.[269] One notable exception is Professor Amy Kapczynski's recent examination of the global influenza virus-sharing network, whose goal is to assist in the development of each year's seasonal flu vaccine.[270] As Kapczynski argues, the flu network "is capital intensive, produces goods of enormous social value, and has operated successfully for decades without any significant recourse to intellectual property rights."[271] This Article advances this line of scholarship, presenting an example to support the proposition that alternative innovation mechanisms can be not only complements to, but substitutes for, the patent system in at least some cases.

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266. This strand of the literature is sometimes called "Innovation Law Beyond IP," after conferences by that name at Yale Law School in 2014 and 2015 designed to showcase work in this field. *See, e.g.*, Eisenberg, *supra* note 74, at 364 (2007); Gallini & Scotchmer, *supra* note 49, at 54–55; Heled, *supra* note 8, at 424; Hemel & Ouellette, *supra* note 38; Kapczynski & Syed, *supra* note 19, at 1907; Lisa Larrimore Ouellette, *Patentable Subject Matter and Nonpatent Innovation Incentives*, 5 U.C. IRVINE L. REV. 1115 (2015); Sachs, *supra* note 3; Brett Frischmann & Mark P. McKenna, *Comparative Analysis of (Innovation) Failures and Institutions in Context* (Sept. 1, 2014) (unpublished manuscript) (on file with author).

267. *See, e.g.*, JESSICA SILBEY, THE EUREKA MYTH: CREATORS, INNOVATORS, AND EVERYDAY INTELLECTUAL PROPERTY (2015); David Fagundes, *Talk Derby to Me: Intellectual Property Norms Governing Roller Derby Pseudonyms*, 90 TEX. L. REV. 1093, 1146 (2012); Dotan Oliar & Christopher Sprigman, *There's No Free Laugh (Anymore): The Emergence of Intellectual Property Norms and the Transformation of Stand-Up Comedy*, 94 VA. L. REV. 1787, 1810 (2008); Aaron Perzanowski, *Tattoos & IP Norms*, 98 MINN. L. REV. 511, 584 (2013).

268. Michael J. Burstein & Fiona E. Murray, *Innovation Prizes in Practice and Theory*, 29 HARV. J.L. & TECH. 401 (2016); John M. Golden & Hannah J. Wiseman, *The Fracking Revolution: Shale Gas as a Case Study in Innovation Policy*, 64 EMORY L.J. 955 (2015).

269. *See, e.g.*, Oliar & Sprigman, *supra* note 267, at 1860–61 (stand-up comedy); Ouellette, *supra* note 266, at 1137–39 (software).

270. Amy Kapczynski, *Order Without Intellectual Property Law: Open Science in Influenza*, 102 CORNELL L. REV. 1539, 1542 (2017).

271. *Id.* at 1547.

Conclusion

This Article has taken advantage of the explosion of interest in a new area of research to test a piece of conventional wisdom that is central to patent law: that if patents are truly needed to incentivize innovation anywhere, it is in the pharmaceutical field. The research presented here demonstrates that patents are not necessary (though they may be useful) to encourage innovation in the microbiome space. And outside the microbiome context, I also argue that patents may be less essential than previously thought to encourage innovation in the biologics industry. As always, more research will be required. Academics who come across other examples of this type ought to pursue these avenues further. But the progress of research in the microbiome field without robust patent protection should be heartening to all scholars of innovation that succeeds even without the protections of traditional intellectual-property law.