

# PATENT LAW'S REPRODUCIBILITY PARADOX

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## ABSTRACT

*Clinical research faces a reproducibility crisis. Many recent clinical and preclinical studies appear to be irreproducible—their results cannot be verified by outside researchers. This is problematic for not only scientific reasons but also legal ones: patents grounded in irreproducible research appear to fail their constitutional bargain of property rights in exchange for working disclosures of inventions. The culprit is likely patent law's doctrine of enablement. Although the doctrine requires patents to enable others to make and use their claimed inventions, current difficulties in applying the doctrine hamper or even actively dissuade reproducible data in patents. This Article assesses the difficulties in reconciling these basic goals of scientific research and patent law. More concretely, it provides several examples of irreproducibility in patents on blockbuster drugs—Premprom, Xigris, Plavix, and Avastin—and discusses some of the social costs of the misalignment between good clinical practice and patent doctrine. Ultimately, this analysis illuminates several current debates concerning innovation policy. It strongly suggests that a proper conception of enablement should take into account after-arising evidence. It also sheds light on the true purpose—and limits—of patent disclosure. And lastly, it untangles the doctrines of enablement and utility.*

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## INTRODUCTION

Clinical research currently faces a reproducibility crisis. Francis S. Collins, the former Director of the National Institutes of Health (NIH), recently voiced the concern “that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring.”<sup>1</sup> An economics review of preclinical research estimated that U.S. researchers spend approximately \$28 billion per year on irreproducible studies.<sup>2</sup> *The Economist* stated bluntly: “Scientists like

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1. Francis S. Collins & Lawrence A. Tabak, *NIH Plans to Enhance Reproducibility*, 505 NATURE 612, 612 (2014).

2. Leonard P. Freedman, Iain M. Cockburn & Timothy S. Simcoe, *The Economics of Reproducibility in Preclinical Research*, PLOS BIOLOGY, June 9, 2015, at 3.

to think of science as self-correcting. To an alarming degree, it is not.”<sup>3</sup> Although reproducibility—the verification of scientific results by outside researchers—lies at the heart of the scientific method,<sup>4</sup> “the checks and balances that once ensured scientific fidelity have been hobbled.”<sup>5</sup> And patent law is at least partly to blame.

Because patents require their inventors to sufficiently disclose their inventions to others—enough to enable their peers to “make and use” their claimed inventions<sup>6</sup>—it would seem that patent law provides a bulwark against irreproducibility. But it does not. To the contrary, the availability of patents for the products of clinical research appears to hamper or even actively dissuade reproducibility.<sup>7</sup> Since

3. *Trouble at the Lab*, ECONOMIST (Oct. 19, 2013), <http://www.economist.com/news/briefing/21588057-scientists-think-science-self-correcting-alarming-degree-it-not-trouble> [https://perma.cc/NHT8-WPW8].

4. See H.M. COLLINS, CHANGING ORDER: REPLICATION AND INDUCTION IN SCIENTIFIC PRACTICE 19 (1992) (“Replication is the scientifically institutionalized counterpart of the stability of perception.”); KARL POPPER, THE LOGIC OF SCIENTIFIC DISCOVERY 9 Routledge Classics (2002) (1959) (“The purpose of this [verification] is to find out how far the new consequences of [a] theory—whatever may be new in what it asserts—stand up to the demands of practice, whether raised by purely scientific experiments, or by practical technological applications.”); Dmitry Karshedt, *Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology’s Compliance with the Enablement Requirement*, 3 HASTINGS SCI. & TECH. L.J. 109, 109 (2011) (“Reproducibility is the touchstone of the scientific method and one of the strongest norms of the research community.”); Sören Sonnenburg et al., *The Need for Open Source Software in Machine Learning*, 8 J. MACH. LEARNING RES. 2443, 2449 (2007) (“In many areas of science it is only when an experiment has been corroborated independently by another group of researchers that it is generally accepted by the scientific community.”); Victoria Stodden, *Reproducing Statistical Results*, 2 ANN. REV. STAT. APPLICATIONS 1, 2–4 (2015) [hereinafter Stodden, *Reproducing Statistical Results*]. Stodden notes:

A fundamental goal of statistics is to ensure the reproducibility of scientific findings. . . . If discoveries are made, it is of great interest to understand whether these findings persist in different samples, which may be drawn from the same or different populations, and potentially with different measurement or estimation techniques. The persistence of findings across different samples is the basis upon which scientific claims are evaluated.

*Id.* at 2. To be clear, reproducibility and replicability are related but distinct concepts, and the differences between them may be nuanced. See generally Chris Drummond, *Replicability Is Not Reproducibility: Nor Is It Good Science*, in PROCEEDINGS OF THE EVALUATION METHODS FOR MACHINE LEARNING WORKSHOP AT THE 26TH ICML, MONTREAL, CANADA (2009) (analyzing the differences between replicability and reproducibility). To the extent these concepts can be separated, this Article focuses on what can be considered classic reproducibility—whether the results of a scientific experiment are, in some greater sense, “true.” See POPPER, *supra*, at 195 (discussing “the idea of a reproducible physical effect—an idea which is closely connected with that of objectivity”).

5. Collins & Tabak, *supra* note 1, at 612.

6. 35 U.S.C. § 112 (2012).

7. See, e.g., *In re ’318 Patent Infringement Litig.*, 583 F.3d 1317, 1327 (Fed. Cir. 2009) (disallowing postapplication evidence to satisfy enablement); *Schering Corp. v. Amgen Inc.*, 222

pharmaceutical manufacturers often structure drug development and clinical research around patent protection,<sup>8</sup> patent law's deficiencies with respect to disclosure encourage manufacturers to engage in research—often, irreproducible research—that satisfies the bare minimum needed to obtain protection. This failure of patent law exacerbates the current real-world reproducibility crisis.<sup>9</sup> This Article is the first to explore how patent law—in particular, the weakness of patent law's enablement doctrine—has contributed to failing standards of scientific integrity despite its constitutional objective “to promote the Progress of Science.”<sup>10</sup>

Ironically, this disconnect stems from the mechanism by which patents are supposed to promote scientific progress: disclosure. Patents serve as a quid pro quo: inventors publicly disclose their inventions in return for exclusionary rights. Patent law, in turn, governs the substance and form of inventors' disclosures.<sup>11</sup> To that end, patent law's

F.3d 1347, 1349 (Fed. Cir. 2000) (allowing an amendment—and rejecting the defendant's theory of invalidity—to redefine a scientifically dynamic claim term); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1988) (rejecting evidence that a patent failed to disclose an important method of practicing the invention).

8. See Eric Budish, Benjamin N. Roin & Heidi Williams, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044, 2045–46 (2015) (describing how the structure of the patent system perverts clinical trial structures).

9. Collins & Tabak, *supra* note 1, at 612 (discussing reproducibility in the context of preclinical drug studies). See generally Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 J. AM. MED. ASS'N 368 (2014) (empirically assessing the reproducibility of new, and presumably patented, drugs); Douglas F. Easton et al., *Gene-Panel Sequencing and the Prediction of Breast Cancer Risk*, 372 NEW ENG. J. MED. 2243 (2015) (analyzing the lack of reproducibility for several patented gene-panel sequencing tests); John P.A. Ioannidis, *Why Most Published Research Findings Are False*, 2 PLOS MED. 696 (2005) [hereinafter Ioannidis, *Research Findings*] (theorizing the irreproducibility of clinical trials for popular drugs); John P.A. Ioannidis, *Contradicted and Initially Stronger Effects in Highly Cited Clinical Research*, 294 J. AM. MED. ASS'N 218 (2005) [hereinafter Ioannidis, *Contradicted Effects*] (examining the irreproducibility of certain high-profile drugs and clinical studies); John P.A. Ioannidis, Evangelina E. Ntzani, Thomas A. Trikalinos & Despina G. Contopoulos-Ioannidis, *Replication Validity of Genetic Association Studies*, 29 NATURE GENETICS 306 (2001) [hereinafter Ioannidis et al., *Replication Validity*] (assessing the same for genetic studies); Joseph Lau, John P.A. Ioannidis & Christopher H. Schmid, *Summing Up Evidence: One Answer Is Not Always Enough*, 351 LANCET 123 (1998) (describing the need for multiple studies to assess reproducibility for patented drugs); Jeffrey T. Leek & Roger D. Peng, *P Values Are Just the Tip of the Iceberg*, 520 NATURE 612 (2015) (recounting the difficulties in using certain statistical measures for biomedical research); Donald W. Light & Joel Lexchin, *Why Do Cancer Drugs Get Such an Easy Ride?*, 350 BMJ h2068 (2015) (examining the role of irreproducibility in patented cancer drugs).

10. U.S. CONST. art. I, § 8, cl. 8.

11. See 35 U.S.C. § 112; *In re Nelson*, 280 F.2d 172, 184 (C.C.P.A. 1960) (“[C]ompliance with section 112 . . . is not directed to the *existence* of usefulness but to what an inventor must disclose as the quid pro quo for patent protection.”).

doctrine of enablement canonically requires patents “to enable any person skilled in the art to which it pertains . . . to make and use” the invention.<sup>12</sup>

But this distillation of enablement complicates as many issues as it simplifies. Courts have long struggled with whether to admit evidence arising *after* the application for a patent to demonstrate its enablement—or lack thereof—at the time of its application.<sup>13</sup> Courts have also had difficulty measuring the breadth of the doctrine: whether it applies to the full scope of a patent’s claims—the metes and bounds of the patent grant—or merely a subset.<sup>14</sup> And the doctrine seems to be confusingly intertwined with another patent law doctrine—utility—that only appears to overlap in narrow cases.<sup>15</sup> Consequently, patent law’s enablement doctrine has failed to address how to treat follow-on, validating research; it is unclear whether such studies can be used as evidence in enablement disputes. And even if they can, courts have struggled to align follow-on research to claim language, utility concerns, and shifting clinical paradigms.

These problems highlight the difference between science’s dynamism—its continuous resolution of prior inconsistencies—and patents’ static nature. The ability to replicate previous results to determine their veracity—scientific reproducibility—makes the canon of scientific knowledge, unlike patent law, an ever-moving target.<sup>16</sup> In particular, several major investigations have found that many large and

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12. 35 U.S.C. § 112(a).

13. See Kevin Emerson Collins, *Enabling After-Arising Technology*, 34 J. CORP. L. 1083, 1098–105 (2009) (discussing this difficulty concerning unforeseeable “after-arising” technology); Robin Feldman, *Rethinking Rights in Biospace*, 79 S. CAL. L. REV. 1, 16 (2005) (“On the question of whether the definition of an invention reaches beyond the state of the art at the time of the invention, the contradictions are most striking in the doctrines related to how far a patent holder can reach toward later inventions.”); Mark A. Lemley, *The Changing Meaning of Patent Claim Terms*, 104 MICH. L. REV. 101, 106–07 (2005) (discussing several cases in which claim terms appear to have changed due to later scientific advances).

14. See Bernard Chao, *The Infringement Continuum*, 35 CARDOZO L. REV. 1359, 1378 (2014) (describing this difficulty as “unworkable”).

15. See *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1355 (Fed. Cir. 1999) (merging the two doctrines where the patent described a “nonsensical” method of operation).

16. See THOMAS S. KUHN, *THE STRUCTURE OF SCIENTIFIC REVOLUTIONS* 111 (3d ed. 1996) (describing normal science as a series of ever-moving “paradigm shifts”); POPPER, *supra* note 4, at 281 (“Science never pursues the illusory aim of making its answers final, or even probable. Its advance is, rather, towards an infinite yet attainable aim: that of ever discovering new, deeper, and more general problems, and of subjecting our ever tentative answers to ever renewed and ever more rigorous tests.”).

expensive clinical research efforts are, in fact, irreproducible.<sup>17</sup> This is particularly problematic for new drugs, where studies mandated—and approved—by the U.S. Food and Drug Administration (FDA) have later been cast into doubt.<sup>18</sup> This has led even the most ardent advocates of administrative-agency-supported science to concede the “troubling frequency of published reports that claim a significant result, but fail to be reproducible.”<sup>19</sup>

Patent law’s lack of concern for reproducibility has therefore had a pernicious effect on the reproducibility of clinical research. Because patent law places time constraints on delaying patent applications, pharmaceutical developers have powerful incentives to apply for patents early, on little and irreproducible data.<sup>20</sup> This, in turn, has encouraged pharmaceutical developers to structure their clinical trials around indications that fall within their patents’ claims, even if such claims cannot be reproduced or are clinically meaningless.<sup>21</sup> Several blockbuster drugs—Prempro, Xigris, Plavix, and Avastin—highlight these difficulties. In each case, the early patenting of the drug, on demonstrably irreproducible data, drove the developer to structure clinical trials for indications that were later withdrawn after coming under FDA scrutiny.<sup>22</sup> This incentive to rush to both the U.S. Patent and Trademark Office (PTO) and the FDA bears significant social costs: it motivates pharmaceutical manufacturers to develop easily

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17. Collins & Tabak, *supra* note 1, at 612–13; Downing et al., *supra* note 9, at 372–76; Easton et al., *supra* note 9, at 2243; Ioannidis, *Contradicted Effects*, *supra* note 9, at 218; Ioannidis et al., *Replication Validity*, *supra* note 9, at 306; Ioannidis, *Research Findings*, *supra* note 9, at 696; Lau, Ioannidis & Schmid, *supra* note 9, at 123; Leek & Peng, *supra* note 9, at 612; Randall J. LeVeque, Ian M. Mitchell & Victoria Stodden, *Reproducible Research for Scientific Computing: Tools and Strategies for Changing the Culture*, COMPUTING SCI. & ENGINEERING, July/Aug. 2005, at 13; Stodden, *Reproducing Statistical Results*, *supra* note 4, at 5–15; Yale Law Sch. Roundtable on Data and Code Sharing, *Reproducible Research*, COMPUTING SCI. & ENGINEERING, Sept./Oct. 2010, at 8; Light & Lexchin, *supra* note 9, at h2068.

18. See, e.g., Ioannidis, *Contradicted Effects*, *supra* note 9, at 220–23 (describing forty-five such studies, including tamoxifen, enalapril, and pravastin).

19. Collins & Tabak, *supra* note 1, at 612.

20. See Christopher A. Cotropia, *The Folly of Early Filing in Patent Law*, 61 HASTINGS L.J. 65, 93–96 (2009) (describing the downsides of early patent filing).

21. Cf. Tito Fojo & David R. Parkinson, *Biologically Targeted Cancer Therapy and Marginal Benefits: Are We Making Too Much of Too Little or Are We Achieving Too Little by Giving Too Much?*, 16 CLINICAL CANCER RES. 5972, 5973 (2010) (criticizing the FDA approval process for narrow therapies of patented medications); Tito Fojo & Christine Grady, *How Much Is Life Worth: Cetuximab, Non-Small Cell Lung Cancer, and the \$440 Billion Question*, 101 J. NAT’L CANCER INST. 1044, 1045 (2009) (questioning the clinical meaningfulness of patented cetuximab).

22. See *infra* Part III.B.

patentable, often futile drugs;<sup>23</sup> it furthers secrecy in clinical trials;<sup>24</sup> and it dissuades competitors from researching alternative uses to known, patented therapeutics.<sup>25</sup> For cancer drugs in particular, this disconnect between easy patenting and difficult clinical trials has encouraged drug manufacturers to develop weak but easily patentable and approvable treatments over more difficult cures and preventative therapeutics.<sup>26</sup> A recent study in the *American Economic Review* calculated the monetary and human cost in this shift: “890,000 lost life-years . . . [valued] on the order of \$89 billion.”<sup>27</sup>

Ultimately, this tension between the enablement doctrine and scientific advancement illuminates several scholarly debates concerning patents as a quid pro quo of property for progress. First, it strongly suggests that enablement should take into account after-arising evidence. Patents with claims that are later to be found to be nakedly irreproducible simply do not enable others to “make and use” them—nor did they at the time the patent was filed. Invalidating claims like these should not turn on whether a follow-on study was published after a patent application was filed. Rather, they should rest on what the after-arising data mean about the invention at the time the invention was created. Relatedly, this suggests that technology-specific effects in patent law can be a normative good.<sup>28</sup> Holding pharmaceutical patents to a higher enablement standard, for example, may encourage better preclinical trials or may shift drug developers’ research priorities to longer-term, more statistically robust projects. Second, this tension demonstrates patents’ limits as vehicles of useful scientific disclosure. Despite some scholars’ advocacy for patents as

23. Budish, Roin & Williams, *supra* note 8, at 2077 (discussing tamoxifen); Fojo & Grady, *supra* note 21, at 1045 (discussing cetuximab).

24. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 382–83 (2007).

25. See *id.* at 370; Anna B. Laakmann, *A Property Theory of Medical Innovation*, 56 JURIMETRICS J. 117, 157–58 (2016). Laakman states:

Firms generally refrain from developing unpatentable inventions, and manufacturers stand to gain little from performing risky, rigorous clinical trials to study off-label uses of licensed drugs. Inherent drawbacks of relying on current market-based mechanisms to encourage the production of this type of information resource make it an attractive target for policy intervention.

*Id.* (footnote omitted).

26. Budish, Roin & Williams, *supra* note 8, at 2049.

27. *Id.*

28. *Contra* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1616–30 (2003).

fonts of scientific information,<sup>29</sup> it seems clear that patents, especially for complex or statistically bound inventions, routinely disclose information that does not meet the strictures of scientific publishing. And third, framing enablement as incongruent with scientific norms suggests an easy distinction between the oft-confused enablement and utility doctrines: claims that are mathematically or physically impossible fail for a lack of utility; claims that are proven wrong or overbroad by a later statistical analysis should fail for a lack of enablement.

Part I of this Article examines the norm and importance of reproducibility in science, as well as recent concerns over irreproducibility, especially in the context of clinical trials. Part II reviews patent law's doctrine of enablement, and its difficulties, with respect to reproducibility. Part III then examines the intersection between enablement and irreproducibility in the context of pharmaceutical patents. It analyzes pharmaceutical developers' incentives to file patents based on irreproducible data. It describes four such cases, all for blockbuster drugs—Prempo, Xigris, Plavix, and Avastin. And it also details some of the social costs of such a system. Lastly, Part IV explains how this Article resolves several current scholarly debates over the role of enablement and disclosure in the patent system.

## I. SCIENTIFIC IRREPRODUCIBILITY

### A. *The Importance of Reproducibility in Science*

Ideally, science proceeds by hypothesis testing—by generating hypotheses about natural phenomena and subjecting those hypotheses to rigorous testing.<sup>30</sup> When testing conclusively confirms or refutes a hypothesis being investigated, scientists will then often report on their findings and subject their report to “peer review,” an assessment by

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29. See, e.g., Sean B. Seymore, *The Teaching Function of Patents*, 85 NOTRE DAME L. REV. 621, 624 (2010).

30. POPPER, *supra* note 4, at 9. Popper writes:

From a new idea, put up tentatively, and not yet justified in any way—an anticipation, a hypothesis, a theoretical system, or what you will—conclusions are drawn by means of logical deduction. . . . [T]here is the testing of the theory by way of empirical applications of the conclusions which can be derived from it. The purpose of this last kind of test is to find out how far the new consequences of the theory—whatever may be new in what it asserts—stand up to the demands of practice, whether raised by purely scientific experiments, or by practical technological applications.

*Id.*



other peer scientists of the testing design, the conduct of the experiments, and the conclusions drawn by the original investigator.<sup>31</sup> Once a report survives peer review—arguably the superlative standard in scientific publishing<sup>32</sup>—other scientists can then adopt and internalize the report's findings.<sup>33</sup> Future scientists may then use the information validated in the original report to generate new hypotheses and to subject those hypotheses to tests, reporting, peer review, and so on. In this way, science carefully and incrementally advances.<sup>34</sup>

In reality, however, science does not ossify around past publications.<sup>35</sup> The skepticism inherent in the scientific method that gives rise to experimentalism and peer review also engenders a ceaseless drive for certainty, even with otherwise strong confirming evidence.<sup>36</sup> In that spirit, scientists often attempt to replicate each other's experiments—both to generate hypotheses of their own and

31. ADIL E. SHAMOO & DAVID B. RESNIK, RESPONSIBLE CONDUCT OF RESEARCH 69–70 (2d ed. 2009) (discussing the components of successful collaboration among scientists).

32. J.B. Ruhl & James Salzman, *In Defense of Regulatory Peer Review*, 84 WASH. U. L. REV. 1, 6 (2006) (“Peer review is commonplace, indeed, fundamental, to the practice of science. It is the gold standard for determining publication and general acceptance of scientific research.”).

33. Effie J. Chan, Note, *The “Brave New World” of Daubert: True Peer Review, Editorial Peer Review, and Scientific Validity*, 70 N.Y.U. L. REV. 100, 114 (1995) (“Scientific progress results when a claim is repeatedly confirmed by the testing of true peer review. . . . It becomes part of the fund of scientific knowledge from which further scientific advances may be made.”).

34. See Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1055 (1989). Eisenberg states:

[F]ree access promotes scientific progress by permitting other scientists to use prior discoveries in subsequent research. . . . It may be that most if not all new discoveries build upon prior discoveries, and that scientists therefore need to use prior discoveries in order to advance the state of scientific knowledge.

*Id.*

35. See LARRY LAUDAN, PROGRESS AND ITS PROBLEMS: TOWARDS A THEORY OF SCIENTIFIC GROWTH 25 (1977). Laudan asserts:

One of the richest and healthiest dimensions of science is the growth through time of the standards it demands for something to count as a solution to a problem. What one generation of scientists will accept as a perfectly adequate solution will often be viewed by the next generation as a hopelessly inadequate one.

*Id.*

36. See Sheila Jasanoff, *Technologies of Humility*, 450 NATURE 33, 33 (2007). Jasanoff states:

The great mystery of modernity is that we think of certainty as an attainable state. Uncertainty has become the threat to collective action, the disease that knowledge must cure. It is the condition that poses cruel dilemmas for decision-makers; that must be reduced at any cost; that is tamed with scenarios and assessments; and that feeds the frenzy for new knowledge, much of it scientific.

*Id.*

also to provide a further check on the peer-review process.<sup>37</sup> The success or failure of these attempts to replicate prior results is often measured as a study's "reproducibility": whether a published experiment is, in fact, reproducible by an independent group of researchers.<sup>38</sup> If a research result is not reproducible—if other investigators cannot obtain the same results as the original investigators, using the same methods—there is good reason to doubt the original result even if the prior work was subjected to the peer-review process.<sup>39</sup> In this way, science is largely self-correcting: "[E]rrors are systematically criticized and fairly often, in time, corrected."<sup>40</sup>

There are countless ways for scientific experiments to fail. And there are myriad ways to assess experiments' reproducibility. Recently, Victoria Stodden has categorized the facets of reproducibility into three groups: empirical reproducibility, statistical reproducibility, and computational reproducibility.<sup>41</sup> Empirical reproducibility is the classical kind: whether, given enough information about an experiment's conditions, parameters, and equipment, an independent researcher can obtain the same results as those previously published.<sup>42</sup> Concerns over this sort of reproducibility date back to at least the seventeenth century, arising from a dispute between Christiaan Huygens and Robert Hooke over the suspension, or lack thereof, of expurgated water in glass columns.<sup>43</sup> Statistical reproducibility, by contrast, concerns whether an experiment can be repeated with the same degree of statistical certainty as its predecessor, or whether the conclusions of the original study's authors were statistically sound.<sup>44</sup> Errors in the application of certain statistical methods, data collection,

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37. See COLLINS, *supra* note 4, at 29–50 (discussing the role of replication in scientific practice). *But see* Eisenberg, *supra* note 34, at 1049–51 (describing the lack of practical incentives for replication studies).

38. See Victoria Stodden, *Reproducibility*, in *THIS IDEA MUST DIE: SCIENTIFIC THEORIES THAT ARE BLOCKING PROGRESS* 529, 529–31 (John Brockman ed., 2015).

39. See Bruce Alberts et al., *Self-Correction in Science at Work*, 348 *SCIENCE* 1420, 1420–22 (2015) (discussing reproducibility as science's "[s]elf-correction" mechanism).

40. *Id.* at 1420 (quoting KARL POPPER, *CONJECTURES AND REFUTATIONS: THE GROWTH OF SCIENTIFIC KNOWLEDGE* 293 (1963)).

41. Stodden, *supra* note 38, at 529–31.

42. *Id.* at 529.

43. ROBERT D. PURRINGTON, *THE FIRST PROFESSIONAL SCIENTIST: ROBERT HOOKE AND THE ROYAL SOCIETY OF LONDON* 48–50 (Eberhard Knobloch, Helge Kragh & Erhard Scholz eds., 2009) (describing the resolution of Huygens's and Hooke's conflicting experiments in the 1660s as the driver for the Royal Society's focus on reproducibility); *see also* Stodden, *supra* note 38, at 529.

44. Stodden, *supra* note 38, at 531.

and sample sizes, for example, can generate statistically irreproducible results.<sup>45</sup> Computational reproducibility is a more modern concern: whether, given “changes in scientific practice and reporting standards to accommodate the use of computational technology . . . the same results can be obtained from the data and code used in the original study.”<sup>46</sup> An increasing number of scientific disciplines—for example, meteorology, astronomy, and molecular biology—rely on code to test hypotheses and generate results. Understanding and being able to use that code has become critical in ascertaining whether previously published results are, in fact, reproducible.<sup>47</sup>

No matter the label, “[t]he ability of other investigators to replicate the experiments by following the method in the published report is crucial to the advancement of science.”<sup>48</sup> It is “the touchstone of the scientific method and one of the strongest norms of the research community.”<sup>49</sup>

### *B Recent Concerns over Irreproducibility*

Recently, several researchers, including the former director of the NIH, Francis S. Collins, voiced their concerns that many peer-reviewed, published scientific studies were irreproducible—or, at the very least, not replicable.<sup>50</sup> Although outright fraud was extremely rare—only twelve cases in 2011 out of thousands of studies performed<sup>51</sup>—Collins and Lawrence A. Tabak, the principal deputy director of the NIH, attributed this crisis in reproducibility to “a complex array of other factors”:

[P]oor training of researchers in experimental design; increased emphasis on making provocative statements rather than presenting

45. Stodden, *Reproducing Statistical Results*, *supra* note 4, at 2–4.

46. *Id.* at 2.

47. Yale Law Sch. Roundtable on Data and Code Sharing, *supra* note 17, at 8 (“Massive computation is transforming science. This is clearly evident from highly visible launches of large-scale data mining and simulation projects such as those in climate change prediction, galaxy formation and biomolecular modeling.” (footnote omitted) (citations omitted)).

48. SHAMOO & RESNIK, *supra* note 31, at 51.

49. Karshedt, *supra* note 4, at 109.

50. *E.g.*, Collins & Tabak, *supra* note 1, at 612; Downing et al., *supra* note 9, at 368; Easton et al., *supra* note 9, at 2243; Ioannidis, *Contradicted Effects*, *supra* note 9, at 218; Ioannidis et al., *Replication Validity*, *supra* note 9, at 306; Ioannidis, *Research Findings*, *supra* note 9, at 696; Lau, Ioannidis & Schmid, *supra* note 9, at 123; Leek & Peng, *supra* note 9, at 612; LeVeque et al., *supra* note 17, at 13; Stodden, *supra* note 4, at 1; Yale Law Sch. Roundtable on Data and Code Sharing, *supra* note 17, at 8; Light & Lexchin, *supra* note 9, at h2068.

51. Collins & Tabak, *supra* note 1, at 612.

technical details; and publications that do not report basic elements of experimental design. Crucial experimental design elements that are all too frequently ignored include blinding, randomization, replication, sample-size calculation and the effect of sex differences. And some scientists reputedly use a ‘secret sauce’ to make their experiments work—and withhold details from publication or describe them only vaguely to retain a competitive edge.<sup>52</sup>

Other researchers have examined these factors in depth. In a famous 2005 article, *Why Most Published Research Findings Are False*, John P.A. Ioannidis claimed, “[F]alse findings may be the majority or even the vast majority of published research claims.”<sup>53</sup> Ioannidis’s article criticized the lack of attention paid to experimental design and attempted to calculate how researcher bias—both statistical and psychological—contributed to such failures.<sup>54</sup> The article developed metrics for assessing a given study’s “pre-study odds”<sup>55</sup>—the likelihood that a study will yield true or reproducible results given its design—with its “positive predictive value” (PPV)—the likelihood that a study is true given the results it generated.<sup>56</sup> Studies with good experimental designs that yield narrow, powerful results are likely to be reproducible. Studies with poor experimental design that yield fantastical results are likely to be just that—fantastical.<sup>57</sup> After assessing various types of studies, Ioannidis concluded that, generally, “a PPV exceeding 50% is quite difficult to get.”<sup>58</sup> In some types of studies, such as “[d]iscovery-oriented exploratory research with massive testing,” Ioannidis calculated the PPV to be 0.1 percent.<sup>59</sup> In other words, each result in such a study is likely to be irreproducible 99.9 percent of the time.<sup>60</sup>

Some of the biases studied by Ioannidis focused on the tools of statistical inquiry themselves.<sup>61</sup> Researchers’ reliance on one such tool,

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52. *Id.* (footnotes omitted).

53. Ioannidis, *Research Findings*, *supra* note 9, at 696.

54. *Id.*

55. *Id.* at 697–98.

56. *Id.* at 696.

57. *Id.* at 700.

58. *Id.* at 699.

59. *Id.* at 700 (calculating the PPV to be 0.1 percent).

60. *Id.*

61. *Id.* at 696–97 (discussing the statistical measurements of error, power, and significance); see also Stodden, *Reproducing Statistical Results*, *supra* note 4, at 1 (discussing statistical irreproducibility).

statistical significance ( $p$ ), has raised some particularly thorny issues of reproducibility. A 1998 study criticized the use of  $p$ -values in meta-analyses of clinical trials.<sup>62</sup> The measurement failed to take into account the heterogeneity of multiple studies, the studies' differences in sample sizes, or certain random effects present in each study.<sup>63</sup> This reliance on  $p$ -values cast doubt on the studies' claims to causality and universality—in other words, the ability of future studies to reproduce the results seen in the aggregate.<sup>64</sup> A similar practice, “ $p$ -hacking,” involves measuring different combinations of variables in the hope that one combination will produce statistically significant results—with reproducibility often a victim.<sup>65</sup> And at its most extreme, researchers' reliance on  $p$ -values has had the effect of creating competing, contradicted studies—later findings that came to the *opposite* conclusions of their predecessors.<sup>66</sup>

Stephen T. Ziliak and Deirdre N. McCloskey have controversially derided this reliance on  $p$ -values as “the cult of  $p$ .”<sup>67</sup> Even the Supreme Court—a court of law, not of math—has cast doubt on  $p$ 's importance. In *Matrixx Initiatives, Inc. v. Siracusano*,<sup>68</sup> the Court allowed shareholders of a drug manufacturer to pursue their securities claims against the company concerning its alleged misrepresentation of its drug's side effects.<sup>69</sup> The Court rejected the company's defense that the lack of statistical significance between ingesting the drug and its side effects meant that such complications were merely “anecdotal.”<sup>70</sup> “This

62. Lau, Ioannidis & Schmid, *supra* note 9, at 125.

63. *Id.* at 124–26.

64. *Id.* at 125.

65. Regina Nuzzo, *Statistical Errors*, 506 NATURE 150, 150–52 (2014) (describing one instance of  $p$ -hacking). For a general overview and estimation of the practice, see generally Megan L. Head et al., *The Extent and Consequences of P-Hacking in Science*, PLOS BIOLOGY, Mar. 13 2015, at 1. For a humorous overview of the practice in clinical health studies, see *Last Week Tonight with John Oliver: Scientific Studies* (HBO television broadcast May 8, 2016).

66. See Ioannidis, *Contradicted Effects*, *supra* note 9, at 223–26 (discussing the factors that contribute to contradicted findings).

67. STEPHEN T. ZILIAK & DEIRDRE N. MCCLOSKEY, THE CULT OF STATISTICAL SIGNIFICANCE: HOW THE STANDARD ERROR COSTS US JOBS, JUSTICE, AND LIVES 9 (2008).

68. *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27 (2011).

69. *Id.* at 30–31.

70. *Id.* at 39–40 (“Absent statistical significance, Matrixx argues, adverse event reports provide only ‘anecdotal’ evidence that ‘the user of a drug experienced an adverse event at some point during or following the use of that drug.’” (quoting Brief for Petitioners at 17, *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27 (2011) (No. 09-1156))).

premise is flawed,” concluded the Court, for many of the same reasons researchers have come to criticize the measurement.<sup>71</sup>

Irreproducibility also stems from what Collins and Tabak dub the “secret sauce,” where researchers “withhold details from publication or describe them only vaguely to retain a competitive edge.”<sup>72</sup> One medical diagnostics company, Theranos, attempted—and spectacularly failed—to bank on this asymmetry, by trying to protect its methods and results as trade secrets rather than subjecting its products to peer review or disclosing them in patents.<sup>73</sup> Researchers criticized the company for engaging in “stealth research,” where there was little hope of having “its methods and technologies scrutinized and validated by independent scientists.”<sup>74</sup> Indeed, it took a comprehensive, long-term investigation by *Wall Street Journal* reporter John Carreyrou to find that many of Theranos’s test results—some of which appeared fraudulent—could not be reproduced by gold-standard, hospital-grade laboratory tests.<sup>75</sup>

In other instances, reproducibility appears impossible because researchers simply refuse to adequately disclose their methods in obtaining computational results.<sup>76</sup> In the precision-medicine context—where scientists attempt to link individual genetic variations to disease—clinicians often rely on “opaque computational models to

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71. See *id.* at 40 (discussing the impossibility of obtaining statistically significant measurements for small samples, alternatives to statistical significance for expert testimony on causation, and the FDA’s use of statistical significance—or lack thereof—for postmarket surveillance of approved drugs).

72. Collins & Tabak, *supra* note 1, at 612 (footnote omitted).

73. John P.A. Ioannidis, *Stealth Research: Is Biomedical Innovation Happening Outside the Peer-Reviewed Literature?*, 313 J. AM. MED. ASS’N 663, 663 (2015).

74. *Id.* at 664.

75. See John Carreyrou, *Hot Startup Theranos Has Struggled with Its Blood-Test Technology*, WALL STREET J. (Oct. 16, 2015, 3:20 PM), <http://www.wsj.com/articles/theranos-has-struggled-with-blood-tests-1444881901> [<https://perma.cc/EFJ4-P579>]. John Carreyrou’s investigation into Theranos’s reproducibility issues and corporate behavior has been a saga unto itself. His work on the Theranos case led the Centers for Medicare and Medicaid Services to propose sanctions on the company for misbehavior. Letter from Karen Fuller, Manager, State Oversight and CLIA Branch, Div. of Survey and Certification, Ctrs. for Medicare & Medicaid Servs., to Sunil Dhawan, Dir., Elizabeth Holmes, Owner, and Ramesh Balwani, President, Theranos, Inc. (Mar. 18, 2016), <http://www.wsj.com/public/resources/documents/hhslettertheranos.pdf> [<https://perma.cc/LPF7-7JBS>]. This reporting garnered Carreyrou the 2015 George Polk Award for Financial Reporting. Press Release, Long Island Univ., Long Island University Announces 67th Annual George Polk Awards in Journalism (Feb. 14, 2016), [http://www.liu.edu/~link.aspx?\\_id=125E54C4CDB14A2E87A9C305A390C0F8&\\_z=z](http://www.liu.edu/~link.aspx?_id=125E54C4CDB14A2E87A9C305A390C0F8&_z=z) [<https://perma.cc/6UFP-YVEP>].

76. Victoria Stodden, *Trust Your Science? Open Your Data and Code*, 2011 AMSTAT NEWS 21, 21; Yale Law Sch. Roundtable on Data and Code Sharing, *supra* note 17, at 8.

make decisions related to health care,” what W. Nicholson Price II calls “black-box medicine.”<sup>77</sup> “Secrecy, however, is a problematic incentive for the datasets underpinning the development of black-box medicine and makes method validation impossible.”<sup>78</sup> Without external validation, any scientific finding using these models simply “retains whatever biases or errors may have created problems in the first place.”<sup>79</sup> And disconcertingly, “the FDA currently lacks the expertise and resources to independently replicate a company’s algorithmic results.”<sup>80</sup>

Even when innovative companies do seek out patents on their work—and, consequently, disclose their methods to the public—follow-on researchers have no greater guarantee that the most important aspects of those companies’ data will be reproducible. Myriad Genetics, for example, patented two genes related to breast cancer risk, *BRCA1* and *BRCA2*, as well as methods of testing them, before having such patents struck down by the Supreme Court.<sup>81</sup> But Myriad kept—and continues to keep—a secret database of numerous variants of those genes in an attempt to command a competitive advantage over its rivals; by having a robust yet confidential database of these “variants of unknown significance,” Myriad hopes to attract clinicians’ business.<sup>82</sup> Secrecy of this sort is simply “not independently verifiable or replicable.”<sup>83</sup> In this way, companies have used patent protection—with its traditional celebration of disclosure—as little more than leverage to protect secret and potentially irreproducible technology.<sup>84</sup>

These concerns with irreproducibility in scientific research are not just limited to problems in methodology. In some instances, the sensitivities of researchers’ physical tools are to blame. One study blamed poor materials as the culprit behind over a third of

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77. W. Nicholson Price II, *Black-Box Medicine*, 28 HARV. J.L. & TECH. 419, 421 (2015).

78. *Id.* at 447.

79. *Id.* at 441.

80. *Id.* at 442.

81. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2120 (2013).

82. John M. Conley, Robert Cook-Deegan & Gabriel Lázaro-Muñoz, *Myriad After Myriad: The Proprietary Data Dilemma*, 15 N.C. J.L. & TECH. 597, 613–16 (2014).

83. *Id.* at 635.

84. Dan L. Burk, *Patents as Data Aggregators in Personalized Medicine*, 21 B.U. J. SCI. TECH. L. 233, 239–240 (2015); Jacob S. Sherkow & Christopher Scott, *Myriad Stands Alone*, 32 NATURE BIOTECHNOLOGY 620, 620 (2014) (discussing Myriad’s patents as forming its secret database). Brenda M. Simon & Ted M. Sichelman, *Data-Generating Patents*, 111 Nw. U. L. REV. (forthcoming 2017), <http://ssrn.com/abstract=2753547> [<https://perma.cc/A3X8-PRY5>].

irreproducible studies.<sup>85</sup> Antibodies—the workhorses of molecular biology, molecules thought capable of uniquely pairing to a single other molecule—have also recently been blamed for a rash of irreproducible studies.<sup>86</sup> Improper use or characterization of antibodies can cause them to react with unintended molecules, resulting in both false positive and false negative results.<sup>87</sup> In other cases, manufacturing variability within a single batch of antibodies can yield different results across different conditions.<sup>88</sup> And even using “good” antibodies, slight changes in experimental conditions can move the needle on certain results.<sup>89</sup> This has led several researchers to speculate that, at least in part, “antibodies are a major driver of what has been deemed a ‘reproducibility crisis,’ a growing realization that the results of many biomedical experiments cannot be reproduced and that the conclusions based on them may be unfounded.”<sup>90</sup>

### C. *Irreproducibility in Clinical Trials*

Although irreproducibility has the potential to threaten all areas of the scientific endeavor, it seems particularly poignant in biomedical research—and for clinical trials in particular.<sup>91</sup> News reports have recently focused on one study that claimed that “[s]cientists in the United States spend \$28 billion each year on basic biomedical research

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85. Monya Baker, *Irreproducible Biology Research Costs Put at \$28 Billion Per Year*, NATURE: NEWS, (June 9, 2015), <http://www.nature.com/news/irreproducible-biology-research-costs-put-at-28-billion-per-year-1.17711> [<https://perma.cc/K4XR-969C>] [hereinafter Baker, *Irreproducible Biology Research*] (“Overall, the team found that poor materials made the largest contribution to reproducibility problems, at 36% . . .”).

86. Monya Baker, *Blame It on the Antibodies*, 521 NATURE 274, 274 (2015) [hereinafter Baker, *Antibodies*].

87. *See id.* at 275–76.

88. *See id.*

89. *See id.*

90. *Id.* at 274.

91. *Id.*; Collins & Tabak, *supra* note 1, at 613 (“The recent evidence showing the irreproducibility of significant numbers of biomedical-research publications demands immediate and substantive action.”); Ioannidis, *Research Findings*, *supra* note 9, at 700 (“As shown, the majority of modern biomedical research is operating in areas with very low pre- and post- study probability for true findings.”); Baker, *Irreproducible Biology Research*, *supra* note 85, at 1; Jocelyn Kaiser, *Study Claims \$28 Billion a Year Spent on Irreproducible Biomedical Research*, SCIENCE (June 9, 2015, 1:30 PM), <http://www.sciencemag.org/news/2015/06/study-claims-28-billion-year-spent-irreproducible-biomedical-research> [<https://perma.cc/ZXC7-5CAS>] (“An eye-popping \$28 billion is spent in the United States each year on preclinical research that can’t be reproduced by other researchers. That’s the conclusion of a provocative analysis published today in part by economists who based it on past studies of error rates in biomedical studies.”)



that cannot be repeated successfully.”<sup>92</sup> The study examined other reports of irreproducibility in an attempt to characterize and quantify their causes, finding that roughly 50 percent of all preclinical cancer studies contained at least one irreproducible result.<sup>93</sup> Given that the United States spends roughly \$56 billion each year on such studies, this amounted, in the authors’ view, to close to \$28 billion of waste.<sup>94</sup> Economics aside, other investigators have delivered damning sermons about reproducibility in biomedical studies, with one report claiming that “47 of 53 landmark cancer research papers could not be reproduced.”<sup>95</sup> Some have focused on irreproducibility as a function of the incentive structure of biomedical research, noting that “[c]onflicts of interest are very common in biomedical research, and . . . inadequately and sparsely reported.”<sup>96</sup> And yet others have pointed to irreproducibility as a symptom of declining morale among biomedical researchers faced with daunting career challenges and, for academic researchers, faced with tenure pressures.<sup>97</sup>

Clinical trials—studies of new drugs or devices to determine their safety and efficacy—seem particularly prone to claims of irreproducibility. Clinical trials often suffer from many of the ills that were found by Ioannidis to give rise to irreproducible results, including small sample sizes, small effects, a larger number of tested variables, an increasing flexibility in design, a greater potential for conflicts of interest, and a higher quotient of competitive popularity.<sup>98</sup> One analysis of forty-nine “highly cited original clinical research studies” found that seven of the follow-on studies—16 percent—wholly contradicted their earlier studies’ findings.<sup>99</sup> In one particularly egregious example, a 1991 clinical trial claimed that postmenopausal women receiving hormone replacement therapy were 44 percent less susceptible to coronary artery disease.<sup>100</sup> A 2002 follow-up trial concluded, much to the contrary, that hormone replacement therapy

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92. Baker, *Irreproducibility Biology Research*, *supra* note 85, at 1.

93. Freedman et al., *supra* note 2, at 3.

94. *Id.*

95. Baker, *Antibodies*, *supra* note 86, at 275.

96. Ioannidis, *Research Findings*, *supra* note 9, at 698.

97. See Alberts et al., *supra* note 39, at 1421.

98. Ioannidis, *Research Findings*, *supra* note 9, at 697–98.

99. Ioannidis, *Contradicted Effects*, *supra* note 9, at 218.

100. See *id.* at 223 n.13 (citing Meir J. Stampfer et al., *Post-Menopausal Estrogen Therapy and Cardiovascular Disease: Ten-Year Follow-Up from the Nurses’ Health Study*, 325 *NEW ENG. J. MED.* 756 (1991) [hereinafter *Nurses’ Health Study*]).

was responsible for a 29 percent *increase* in coronary artery disease.<sup>101</sup> Even where follow-on clinical trials do not contradict their predecessors, they may find no evidence to support the original study's results, or find that the level of effect reported by the previous study was, in fact, substantially incorrect. Of the same forty-nine original clinical research studies, four found little evidence to verify the original clinical trials' claims, while another seven concluded that the original study found substantially higher efficacy than warranted.<sup>102</sup> In all, eighteen of the forty-nine clinical trials, or 36.7 percent, could not be reproduced.<sup>103</sup> Perhaps equally concerning is that, to date, eleven of the original forty-nine clinical trials have yet to be challenged in any way.<sup>104</sup>

Because clinical trials are almost always conducted for the purpose of receiving FDA approval to market a particular therapy, some of these failures in reproducibility stem from the agency's standards for clinical trials.<sup>105</sup> An exhaustive 2014 study that revisited the clinical trial data for all new drugs approved by the FDA from 2005 to 2012 concluded that "[t]he quality of clinical trial evidence used by the FDA as the basis for recent approvals of novel therapeutic agents varied widely across indications."<sup>106</sup> Some of this flexibility is the product of necessity; "A perfect gold standard is not possible in clinical research."<sup>107</sup> Some may even "be warranted given the limited number of effective therapies and the poor prognosis associated with [diseases like] cancer."<sup>108</sup>

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101. *Id.* at 223 n.44 (discussing Writing Grp. for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 J. AM. MED. ASS'N 321 (2002) [hereinafter *Women's Health Initiative Study*]). Perhaps unsurprisingly, this seventy-three-percentage-point swing resulted in a substantial products-liability lawsuit against the therapy's manufacturer, Wyeth Pharmaceuticals. See Tobias Millrood, *The Rise and Fall of Hormone Therapy*, TRIAL, Aug. 2003, at 43–47 (describing class action litigation that resulted from health risks associated with the drug Prempro).

102. Ioannidis, *Contradicted Effects*, *supra* note 9, at 222.

103. *Id.* This can be calculated by adding the number of clinical trials where later research has demonstrated a contradicted effect (seven), no effect (four), or a substantially diminished effect (seven).

104. *Id.* at 218.

105. Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE L. REV. 2073, 2093–95 (2013) (discussing the deficiencies in the FDA's standards for clinical trials).

106. Downing et al., *supra* note 9, at 368.

107. Ioannidis, *Contradicted Effects*, *supra* note 9, at 224.

108. Downing et al., *supra* note 9, at 373.

Nonetheless, several of the measurements allowed by the FDA to prove efficacy are particularly suspect. The use of surrogate rather than clinical end points—for example, measures of disease progression like the size of patients' tumors as opposed to patients' ultimate survival rates—stands out as a significant source of irreproducibility.<sup>109</sup> “This reliance on surrogate outcomes leaves patients and physicians to extrapolate clinical benefits from trials, again raising questions about the certainty of the medications' benefits in practice,”<sup>110</sup> that is, that such results are not, in fact, real. Even clinical trials that do measure clinical end points like survival times often suffer from low effect sizes, a hallmark of irreproducible results.<sup>111</sup> In the cancer context, subjects for seventy-one solid-tumor drugs approved by the FDA from 2002 to 2014 improved their life span, at median, by only two-and-a-half months.<sup>112</sup> Genetic-association studies—studies attempting to link an individual's risk of developing a genetic disease, such as cancer, with a particular genetic variation—suffer from low effect sizes as well. What is more, attempts to replicate even successful studies have been met with skepticism if not outright backlash.<sup>113</sup>

A lack of statistical power—the capacity of a study to detect the effect of a change on a studied population—appears to be another significant cause of irreproducible results in clinical studies. A 2001 study of thirty-six genetic disease associations found that “[o]ften genetic associations of disease are of modest magnitude . . . and single studies are underpowered to detect them.”<sup>114</sup> This lack of power contributed to the irreproducibility of prior studies linking certain gene variants to schizophrenia, dementia, hypertension, Parkinson disease, lung cancer, alcoholism, diabetic nephropathy, and others.<sup>115</sup> Another

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109. *Id.* at 374.

110. *Id.*

111. See Ioannidis, *Research Findings*, *supra* note 9, at 697 (“The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.”).

112. Light & Lexchin, *supra* note 9, at h2068 (“The 71 drugs approved by the FDA from 2002 to 2014 for solid tumours have resulted in median gains in progression-free and overall survival of only 2.5 and 2.1 months, respectively.” (footnote omitted)). A similar subset of drugs approved by the European Medicines Agency found only a one-and-a-half-month gain. *Id.* (“A review of drugs for solid cancers approved by the European Medicines Agency (EMA) in its first 10 years found that, overall, new oncology drugs improved survival by a mean and median of 1.5 and 1.2 months, respectively.” (footnote omitted)).

113. See Kaiser, *supra* note 91 (describing efforts to replicate successful studies that have been met with skepticism).

114. Ioannidis et al., *Replication Validity*, *supra* note 9, at 308.

115. *Id.* at 307. The authors note:

study of commercially available multigene diagnostic tests casts doubt on the linkages between over a dozen genes analyzed by such services and cancer risk.<sup>116</sup> Of the eleven commercial tests analyzed, every one tested for at least one such dubious genetic variant.<sup>117</sup>

And yet, even when clinical trials meet the “gold standard” in terms of experimental design and predictive power,<sup>118</sup> there is little guarantee that future trials will be able to reproduce their results. Jonathan J. Darrow has noted that “the statistical framework supporting the gold standard does not account for the possibility that drug companies may undertake multiple trials until one or more of them demonstrates efficacy.”<sup>119</sup> Furthermore, even the gold standard is, itself, “inadequate because its statistical framework requires no particular level of efficacy.”<sup>120</sup> In other words, even new drug applicants who adhere to the gold standard to conduct clinical trials are still free to employ a spaghetti-method approach to demonstrate efficacy—where “efficacy” is “not the drug’s level of efficacy *per se*, but rather the [statistical] relationship between the results from the control group and those from the active group.”<sup>121</sup> This nuanced form of *p*-hacking leads Darrow to conclude that the FDA’s “standard[s], along with the related concepts of gold standard testing, statistical significance, and clinical significance, do not prevent FDA approval of substantially ineffective remedies.”<sup>122</sup>

Ultimately, quantifying the amount of irreproducibility in clinical trials may simply be impossible. Not every clinical trial is validated with

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Subsequent studies have failed to validate the originally proposed importance of dopamine receptor D3 gene polymorphisms for schizophrenia, of apolipoprotein E gene polymorphisms for dementia in patients with Down syndrome, of angiotensinogen gene polymorphisms for essential hypertension, of cytochrome p450 2D6 (*CYP2D6*) gene mutations for Parkinson disease or of *CYP2D6* metabolic status for lung cancer. Subsequent studies have confirmed that glutathione S-transferase M1 status may be important in susceptibility to lung cancer, that dopamine receptor D2 gene polymorphisms may confer some susceptibility to alcoholism and that angiotensin-converting enzyme gene polymorphisms may be involved in diabetic nephropathy; however, the strength of the associations found by the subsequent studies is significantly smaller than that postulated by the first studies for each of these three subjects.

*Id.*

116. See Easton et al., *supra* note 9, at 2254.

117. *Id.* at 2242.

118. Darrow, *supra* note 105, at 2090 (enumerating several “gold standard[s]” in clinical trials: “randomization, double-blind administration, and placebo-control”).

119. *Id.* at 2095.

120. *Id.*

121. *Id.* at 2112.

122. *Id.* at 2076.

its own follow-on study, that, in any event, may suffer from its own deficiencies.<sup>123</sup> Clinical trials—and even follow-on trials—are often conducted under the guise of FDA regulations, which have an instrumental rather than an investigatory bent.<sup>124</sup> And new drug applicants can often keep their most damning negative results confidential under the FDA's own regulations.<sup>125</sup> As a result, “noncommercial researchers deprived of the means to independently re-analyze raw data cannot easily verify or refute product sponsors’ safety and efficacy claims.”<sup>126</sup>

## II. IRREPRODUCIBILITY, DISCLOSURE, AND ENABLEMENT

A lack of adequate disclosure accounts for much of today's irreproducible research. The opacity of experimental design, the absence of technical details, and the convolution of statistical calculations all contribute to making follow-on research more difficult to perform and past research difficult to verify.<sup>127</sup> To that end, patents may seem like a cure. Patents have long been described as a *quid pro quo*: the government grants to inventors the exclusive rights to their inventions only so long as they sufficiently disclose them.<sup>128</sup> With an inventor's disclosure, the public receives the technical knowledge contained in the patent as soon as it is published. And after the patent

123. Ioannidis, *Contradicted Effects*, *supra* note 9, at 218.

124. Darrow, *supra* note 105, at 2075–76.

125. Eisenberg, *supra* note 24, at 382–83.

126. Laakmann, *supra* note 25, at 133.

127. *See supra* Part I.

128. The first use of “*quid pro quo*” to describe this disclosure requirement was likely by Chief Judge William C. Coleman of the U.S. District Court for the District of Maryland in *Phillips Petroleum Co. v. Esso Standard Oil Co.* in 1950 and famously repeated ten years later by the U.S. Court of Customs and Patent Appeals in *In re Nelson*. Compare *Phillips Petroleum Co. v. Esso Standard Oil Co.*, 91 F. Supp. 218, 222 (D. Md. 1950) (“But the *quid pro quo* is disclosure of a process or device in sufficient detail to enable one skilled in the art to practice the invention once the period of the monopoly has expired . . .”), with *In re Nelson*, 280 F.2d 172, 184 (C.C.P.A. 1960) (“[C]ompliance with section 112 . . . is not directed to the *existence* of usefulness but to what an inventor must disclose as the *quid pro quo* for patent protection.”). Earlier cases, however, referred to the “*quid*” in the *quid pro quo* as the creation of something previously unknown to the public—not necessarily fully disclosing it. *See, e.g.*, *Pennock v. Dialogue*, 27 U.S. (2 Pet.) 1, 23 (1829). The Court in *Pennock* notes:

If the public were already in possession and common use of an invention fairly and without fraud, there might be sound reason for presuming, that the legislature did not intend to grant an exclusive right to any one to monopolize that which was already common. There would be no *quid pro quo*—no price for the exclusive right or monopoly conferred upon the inventor for fourteen years.

*Id.*

has expired, the public may then use and improve the invention without paying a royalty.<sup>129</sup> This incentive to transfer knowledge is—at least, ideally—the mechanism by which patents “promote the Progress of Science and useful Arts.”<sup>130</sup>

What constitutes a sufficient disclosure, however, is difficult to gauge. A patent that no one can practice makes the disclosure mechanism worthless—and the exclusive grant to the inventor rather costly.<sup>131</sup> At the same time, the lay public cannot be expected to understand even valuable patent disclosures in highly technical fields.<sup>132</sup> Garage-shop tinkerers are not expected to understand patents in the rocket sciences; rocket scientists’ patents should not be invalid for failing to educate them.

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129. See Eisenberg, *supra* note 34, at 1022 (“This enabling disclosure becomes freely available to the public as soon as the patent issues; the patent holder may not thereafter monitor or control access to it.”); Jeanne C. Fromer, *Patent Disclosure*, 94 IOWA L. REV. 539, 548 (2009) (“[Patent disclosure] permits society at large to apply the information by freely making or using the patented invention after the expiration of the patent.”); Timothy R. Holbrook, *Possession in Patent Law*, 59 SMU L. REV. 123, 131 (2006) (“[T]he public benefits from the disclosure of the invention because the public storehouse of knowledge is thus enhanced, allowing others to rely upon the teachings of the patent to generate even further, follow-on innovation.”); Seymore, *supra* note 29, at 624 (“[T]he technical information disclosed in the patent document has potential immediate value to the public, which can use the information for any purpose that does not infringe upon the claims.” (footnote omitted)).

130. U.S. CONST. art. I, § 8, cl. 8. Whether this ideal holds up in practice remains controversial. See, e.g., Burk & Lemley, *supra* note 28, at 1623 (explaining that secrecy, rather than disclosure, facilitates software innovation); Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 177, 198–200 (1987) (arguing that publication norms in scientific research facilitate disclosure more than the patent system); Katherine J. Strandburg, *Users as Innovators: Implications for Patent Doctrine*, 79 U. COLO. L. REV. 467, 485–88 (2008) (proposing that user-innovators’ disclosure preferences are not matched by the patent system).

131. See Fromer, *supra* note 129, at 552–53. Fromer notes:

[P]atentees rationally have little to no incentive to offer more information than the patent laws require and have an incentive to obfuscate information they provide whenever possible. Inventors can seek to maximize their own competitive advantage by curtailing competitors’ use of information about the invention. In this way, they can make it harder for competitors to capitalize on the invention or related technologies, especially when the invention is groundbreaking. . . . These effects serve to prolong the inventors’ exclusive use, thereby enriching the original inventors.

*Id.* (footnotes omitted).

132. See Timothy R. Holbrook, *Patents, Presumptions, and Public Notice*, 86 IND. L.J. 779, 785–87 (2011) (describing the complexities—legal and technical—of disclosures in patents); Mark D. Janis & Timothy R. Holbrook, *Patent Law’s Audience*, 97 MINN. L. REV. 72, 114 n.152 (2012) (“If the law required that the general public be able to read the patent and understand the invention based on little more than the patent document alone, every patent document would need to be a textbook on elementary concepts in order to satisfy the disclosure requirements.”); Seymore, *supra* note 29, at 624–25 (describing the patent document as a potential, and routinely unfulfilled, source of technical information).

The patent statute, title 35 of the U.S. Code, has therefore crafted the bargain that sufficient disclosures are those that “enable any person *skilled in the art* to which [the patent] pertains, or with which it is most nearly connected, to make and use the same.”<sup>133</sup> Whether a patent accomplishes this turns on whether a person skilled in the art would need to engage in “undue experimentation” to practice the invention as described.<sup>134</sup> Distinguishing undue experimentation from the merely routine requires an analysis of both the patent itself as well as the relevant art: the breadth of the patent’s claims, the nature of the invention, the state of prior art, the level of ordinary skill in the field, the art’s predictability, the amount of direction provided in the patent’s written description, whether any working examples exist, and the quantity of experimentation needed to successfully practice the invention.<sup>135</sup> In all, enablement acts as one of “the most important patent doctrine[s],” serving multiple functions: “adequacy of disclosure, . . . the line of demarcation between the visionary theorist . . . and the visionary pioneer[,] . . . [and] the boundary between pioneer inventions and patentable improvements.”<sup>136</sup>

This doctrinal complexity, however, fails to encourage reproducibility in patented disclosures. First, the Federal Circuit has presented conflicting views on whether evidence obtained after a patent application has been filed, such as follow-on research, can be used to prove (or disprove) enablement.<sup>137</sup> This means that advances in science—important in verifying the research underlying a patented invention—can only rarely be used in assessing the scientific validity of

133. 35 U.S.C. § 112(a) (2012) (emphasis added).

134. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

135. *Id.* Notably, these factors are “illustrative, not mandatory.” *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). This analysis makes “[e]nablement, while conceptually simple . . . legally and factually complex.” Holbrook, *supra* note 129, at 129.

136. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 982 (Fed. Cir. 2002) (Rader, J., dissenting); see also Rebecca S. Eisenberg & Robert P. Merges, *Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences*, 23 AIPLA Q.J. 1, 38 (1995) (“Enablement is a particularly important limitation on the patentability of prophetic claims to inventions that the applicant has not yet actually reduced to practice.”); Oskar Liivak, *Rescuing the Invention from the Cult of the Claim*, 42 SETON HALL L. REV. 1, 13 (2012) (proposing that courts’ focus on claim language “assigns a very important role to enablement”); Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1050 (2003) (calling enablement “[t]he most important component of adequate disclosure”).

137. *Compare In re ’318 Patent Infringement Litig.*, 583 F.3d 1317, 1327 (Fed. Cir. 2009) (disallowing future evidence to satisfy enablement), *with Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917, 925–26 (Fed. Cir. 2011) (allowing future evidence to satisfy enablement).

a patent's claims.<sup>138</sup> Second, the Federal Circuit has cobbled together a fractured jurisprudence on the scope, and consequently the verifiability, of the enablement determination—whether, for example, the full scope of a patent's claims must be enabled or only a single embodiment.<sup>139</sup> And third, in some instances, courts have confusingly amalgamated some aspects of enablement with a different patent doctrine, utility, creating a peculiar hybrid doctrine, “enablement utility,” that weakens the relationship between disclosure and reproducibility.<sup>140</sup> These problems each show the difficulties in applying the enablement doctrine to evolving information and aligning patent law with ideals of reproducibility.

#### A. *Postapplication Evidence for Demonstrating Enablement*

There is an inherent disconnect between reproducibility and enablement. Reproducibility looks forward, assessing whether a prior study can be replicated in the future.<sup>141</sup> But the “enablement determination is made *retrospectively*, that is, by looking back to the filing date of the patent application and determining whether undue experimentation *would have been* required to make and use the claimed invention at that time.”<sup>142</sup> The PTO and federal courts do not, in theory, account for later developments in the art that would have enabled an otherwise defective patent application.<sup>143</sup> This suggests that

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138. See Collins, *supra* note 13, at 1098–1105 (discussing this difficulty concerning unforeseeable “after-arising” technology); Feldman, *supra* note 13, at 16 (“On the question of whether the definition of an invention reaches beyond the state of the art at the time of the invention, the contradictions are most striking in the doctrines related to how far a patent holder can reach toward later inventions.”); Lemley, *supra* note 13, at 106–07 (discussing several cases in which claim terms appear to have changed due to later scientific advances).

139. Compare *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012) (invalidating a patent for failing to fully enable the broad scope of its claims), with *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991) (concluding that the enablement requirement is satisfied “if the description enables *any* mode of making and using the claimed invention” (emphasis added)).

140. See *Eli Lilly*, 435 F. App'x at 925–26.

141. See *supra* notes 30–40 and accompanying text.

142. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371–72 (Fed. Cir. 1999).

143. See Collins, *supra* note 13, at 1087. Collins notes:

Because [after-arising technology] is by definition a technology that is not invented until after a patent application has been filed, it is difficult to understand how a specification can teach the [person having ordinary skill in the art] at the time of filing how to make and use [after-arising technology]. This conceptual difficulty has created a problem in contemporary patent law when literal claims encompass [after-arising technology].



enablement is, in fact, less concerned with whether an invention actually works and more concerned with the “draftsman’s art”<sup>144</sup> of describing the invention as far along in the research process.

In *In re '318 Patent Infringement Litigation*,<sup>145</sup> for example, the Federal Circuit affirmed the invalidation of the plaintiffs’ patent covering a method of treating Alzheimer’s disease using galantamine,<sup>146</sup> a common alkaloid extracted from various flowers.<sup>147</sup> The patent application at issue “conclu[ded] that it was possible to administer ‘an effective Alzheimer’s disease cognitively-enhancing amount of galanthamine [sic]’” on the basis of “short summaries of six scientific papers in which galantamine had been administered to humans or animals.”<sup>148</sup> This, the Federal Circuit concluded, was a “mere research proposal”<sup>149</sup> that “did not ‘teach one of skill in the art how to use the claimed method’ because the application ‘only surmise[d] how the claimed method could be used’ without providing sufficient galantamine dosage information.”<sup>150</sup> The fact that later studies proved the inventor’s hypothesis true,<sup>151</sup> or that the FDA eventually approved galantamine to treat Alzheimer’s,<sup>152</sup> was irrelevant.

But later research that illuminates a patent’s claims is not always irrelevant. In *Eli Lilly & Co. v. Actavis Elizabeth LLC*,<sup>153</sup> the Federal Circuit reversed the district court’s conclusion that Eli Lilly’s patent

*Id.*; see Sean B. Seymore, *Heightened Enablement in the Unpredictable Arts*, 56 UCLA L. REV. 127, 142 (2008) (“[T]he Examiner cannot use a reference to show lack of enablement based on later developments in the art.”).

144. *Cf.* *Parker v. Flook*, 437 U.S. 584, 593 (1978) (noting that the need to describe what is being patented precedes the need to argue the discovery’s newness or obviousness).

145. *In re '318 Patent Infringement Litig.*, 583 F.3d 1317 (Fed. Cir. 2009).

146. *Id.* at 1327–28.

147. See Michael Heinrich, *Snowdrops: The Heralds of Spring and a Modern Drug for Alzheimer’s Disease*, 273 PHARMACEUTICAL J. 905, 905 (2004).

148. *In re '318 Patent*, 583 F.3d at 1321 (citations omitted).

149. *Id.* at 1324.

150. *Id.* at 1323 (alterations in original) (quoting *In re '318 Patent Infringement Litig.*, 578 F. Supp. 2d 711, 736 (D. Del. 2008)).

151. See *id.* at 1328 (Gajarsa, J., dissenting) (“[L]ater animal studies and human clinical trials proved and confirmed galantamine’s effectiveness.”).

152. Letter from Robert Temple, M.D., Dir., Office of Drug Evaluation I, Ctr. for Drug Evaluation & Research, to Charles LaPree, Assistant Dir., Regulatory Affairs, Janssen Research Found. (Feb. 28, 2001), [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2001/21169ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2001/21169ltr.pdf) [<https://perma.cc/V9X2-3RPQ>].

153. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917 (Fed. Cir. 2011).

was invalid for lacking enablement.<sup>154</sup> The patent covered a method for treating attention deficit hyperactivity disorder (ADHD) using a newly created drug, atomoxetine.<sup>155</sup> After a bench trial, the district court concluded that the patent was invalid for lacking enablement: “[T]he prior art stressed that the mechanism of action of ADHD was unclear at the time the patent application was filed,”<sup>156</sup> the “patent contained no test data,”<sup>157</sup> and clinical trials had yet to be performed.<sup>158</sup> Even the inventor testified at his deposition, “I wasn’t sure at all that it would work.”<sup>159</sup> But the Federal Circuit reversed the district court’s finding of invalidity because “[clinical trial] data were obtained shortly after the patent application was filed” and “experimental verification was obtained soon after the [patent application’s] filing.”<sup>160</sup> This odd sequence of proof was necessary, in the appellate court’s view, because both scientific methodology and the PTO’s examining procedures commanded it. The former because “[s]cientific methodology today is based on generating hypotheses and testing them to see if they can be falsified.”<sup>161</sup> And the latter because the utility of the invention was “not so incredible as to warrant the special procedures . . . for subject matter in once notoriously intractable [research] areas.”<sup>162</sup>

Reconciling these two cases—and developing a working standard for when enablement can be demonstrated with postapplication evidence—remains difficult. Indeed, it highlights the disconnect between patent law’s enablement doctrine and standards of reproducibility. The patents in both cases were based on thin preclinical trial data. But in both cases, the preclinical trial data had been verified through later, more robust clinical experiments. Yet the different patent-validity outcomes between the two cases turned on the courts’ interpretations of whether there existed, at the time of the

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154. *Id.* at 927.

155. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 731 F. Supp. 2d 348, 351–52 (D.N.J. 2010), *aff’d in part and rev’d in part*, 435 F. App’x 917 (Fed. Cir. 2011).

156. *Id.* at 386.

157. *Id.* at 389.

158. *Id.* at 387–88.

159. *Eli Lilly*, 435 F. App’x at 923.

160. *Id.* at 924.

161. *Id.* (quoting Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 NW. U. L. REV. 643, 645 (1992)).

162. *Id.*

patent applications, “a *reasonable* correlation between [the] compound’s activity and its asserted therapeutic use.”<sup>163</sup>

This reasonable-correlation analysis focused not on whether the patents’ claims were likely to be *reproducible*, that is, *true*, but instead on whether they *reasonably described* a *plausible* therapeutic relationship.<sup>164</sup> This reasonable-correlation standard—however grounded in formalistic patent doctrine—has little to commend it from a reproducibility perspective. Even if a patent application suggests a therapeutic correlation concerning a related but different drug than the one claimed, one would still need to engage in burdensome experimentation—gold-standard clinical trials—to determine whether the claimed drug indeed works as indicated. This was evident for the drugs in both *In re ’318 Patent* and *Eli Lilly*: the patent owners still needed to shepherd their drugs through years of clinical trials simply to determine whether they worked at all.<sup>165</sup>

Similarly, advances in science may change the meaning of claim terms long after the ink has dried on the patent document.<sup>166</sup> Courts interpreting claim terms with a particular scientific meaning are therefore confronted with several difficulties of time: whether to interpret those terms at the time of the patent application, at issuance, or after the patent has issued; whether to allow claim terms to shift meaning from one time to another; and whether others seeking to

163. *Id.* at 926 (emphasis added) (quoting U.S. PATENT & TRADEMARK OFFICE, U.S. DEP’T OF COMMERCE, MANUAL OF PATENT EXAMINING PROCEDURE § 2107.03 (11th ed. 2013) [hereinafter MPEP]) (distinguishing *In re ’318 Patent Infringement Litig.*, 583 F.3d 1317, 1321 (Fed. Cir. 2009)).

164. *See id.*

165. *See In re ’318 Patent*, 583 F.3d at 1328 (Gajarsa, J., dissenting) (“[L]ater animal studies and human clinical trials proved and confirmed galantamine’s effectiveness.”); *Eli Lilly*, 435 F. App’x at 919–20 (recounting the clinical trial history of atomoxetine).

166. *See, e.g., Bayer CropScience AG v. Dow AgroSciences LLC*, 728 F.3d 1324, 1325 (Fed. Cir. 2013) (revisiting the meaning of the term “monooxygenase”); *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1349 (Fed. Cir. 2000) (discussing the history of IFN- $\alpha$ -1); *In re Hogan*, 559 F.2d 595, 597, 608–09 (C.C.P.A. 1977) (reversing the examiner’s rejection on the ground that the term “normally solid homopolymer” had, since the time of filing, become indefinite); *see also* Dan L. Burk, *Edifying Thoughts of a Patent Watcher: The Nature of DNA*, 60 UCLA L. REV. DISCOURSE 92, 95 (2013). Burk notes:

The concept of a gene is entirely a human construct, and there is considerable room for debate as to what ought to be included in the concept of the gene, or, by the same token, what ought to be excluded from the concept of the gene. Some such constructs are more useful to humans than others, but the constructs themselves change over time, resulting in what we term scientific progress—we add or revise or amend the criteria for our constructs, subject to an array of social choices that yield amended or revised or additional outcomes.

*Id.* (footnote omitted).

practice the patent would have recognized such shifts—and, if so, when.

*Schering Corp. v. Amgen Inc.*<sup>167</sup> presents one of the starkest examples of these interpretive difficulties. In 1980, the patentee in *Schering*, Charles Weissmann, invented recombinant versions of a protein then known to scientists as “interferon,” an important component of the human body’s response to viral (and other) infections.<sup>168</sup> His claims were accordingly limited to recombinant molecules of “interferon” and their attendant DNA sequences.<sup>169</sup> Almost immediately after Weissmann applied for his patent, however, scientific advances confirmed that what was previously known as “interferon” was actually a collection of several proteins, later named interferons alpha (IFN- $\alpha$ ), beta (IFN- $\beta$ ), and gamma (IFN- $\gamma$ ). Each of these, in turn, was comprised of various subtypes, IFN- $\alpha$ -1, IFN- $\alpha$ -2, and so on.<sup>170</sup> Now understanding that his recombinant protein referred to a single one of these subtypes—IFN- $\alpha$ -1—Weissmann amended his patent’s claims, changing “interferon” to “IFN- $\alpha$ -1.”<sup>171</sup> In an infringement suit between the patent’s eventual assignee, Schering Corp., and Amgen Inc., the district court concluded that Weissmann’s amendment “did not merely replace the outdated term ‘leukocyte interferon.’ Rather, according to the trial court, the substitution imported years of scientific advance into the ‘901 patent’s disclosure and claims”—an act prohibited under the patent statute.<sup>172</sup> Although the Federal Circuit disagreed with the district court’s interpretation of Weissmann’s patent, it ultimately affirmed the district court’s finding of noninfringement: if IFN- $\alpha$ -1 meant *only* IFN- $\alpha$ -1, Schering recognized that it could not prevail at trial.<sup>173</sup>

*Schering* highlights several of the difficulties of assessing enablement when courts confront claim terms with evolving scientific meanings.<sup>174</sup> In these evolving-meaning cases, both the district and the appellate courts need to determine whether there is a salient difference

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167. *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347 (Fed. Cir. 2000).

168. *See id.* at 1349–50 (“[I]nterferons have important anti-viral and anti-tumor properties.”); *see also* STEPHEN S. HALL, A COMMOTION IN THE BLOOD: LIFE, DEATH, AND THE IMMUNE SYSTEM 131–58 (1997) (discussing the history of the discovery of interferon).

169. *Schering*, 222 F.3d at 1350.

170. *See id.* at 1349, 1352; HALL, *supra* note 168, at 178–208.

171. *Schering*, 222 F.3d at 1352.

172. *Id.*

173. *Id.* at 1349.

174. *See id.* at 1353 (“The scientific meaning of ‘IFN- $\alpha$ ’ evolved with new discoveries.”).

between the disputed claim term—as used in the patent—and the term as understood in the scientific community after the patent had been filed. Without such a difference, the term's definitional shift would not appear to alter the court's invalidity or infringement analyses. In *Schering*, for example, had Weissmann's particular use of the term "interferon" been equivalent to his colleagues' understanding of "IFN- $\alpha$ -1," then it would have mattered little whether a scientific understanding of "interferon" had changed over time. This determination is bound up with determining what aspects of the invention the inventor possessed at the time of filing,<sup>175</sup> an analysis criticized by Robin Feldman as future "assumptions about how far a particular invention can reach."<sup>176</sup>

Courts must also determine when such a shift has occurred: whether prior to issuance or during patent prosecution—when, presumably, the inventor could have amended his claims—or much later, when presumably little could be done.<sup>177</sup> Weissmann's amendments in *Schering* were just that—amendments that he made during the prosecution of the patent—and he was therefore bound to the court's ultimate infringement analysis.<sup>178</sup> In another case, *Bayer CropScience AG v. Dow AgroSciences LLC*,<sup>179</sup> the patentee had not been so swift.<sup>180</sup> There, the parties disputed when the patentees became aware that their use of the term "monooxygenase" had been essentially proven incorrect by later research.<sup>181</sup> The Federal Circuit ultimately held this lapse against the patent owner and affirmed the district court's invalidation of the patent.<sup>182</sup> To resolve this apparent dichotomy, Mark

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175. See Holbrook, *supra* note 129, at 132–33 (discussing the intersection of enablement and possession).

176. Feldman, *supra* note 13, at 25.

177. Even after a patent issues, however, a patentee is entitled to a "reissuance" of his original patent if, "through error, [the patent is] deemed wholly or partly inoperative or invalid, by reason of a defective specification or drawing," 35 U.S.C. § 251(a) (2012). But it is unclear whether a scientifically evolving claim term constitutes "error," as used in the statute. Generally speaking, the error must be inadvertent and the new claims must limit themselves to the same invention as the original application. See Laura A. Bauer, *Modified Reissue Practice*, 8 FED. CIR. B.J. 193, 195, 200–01 (1999).

178. See *Schering*, 222 F.3d at 1353.

179. *Bayer CropScience AG v. Dow AgroSciences LLC*, 728 F.3d 1324 (Fed. Cir. 2013).

180. *Id.* at 1328–29.

181. *Id.*

182. *Id.* at 1332.

A. Lemley has strongly argued to fix these inquiries—and the meaning of claim terms—on the date of the patent application.<sup>183</sup>

Lastly, *Schering* demonstrates some of the procedural difficulties in making such nuanced assessments about the evolving scientific meaning of claim terms. According to Lemley,

Doing so would require the scope of patents to change over time, not only for infringement purposes . . . but also for validity purposes. . . . Even after it issued, a patent's scope would not be fixed, but could differ from infringer to infringer as time passes. As a result, the same patent could be valid at certain times and invalid at others, depending on the meaning of terms at the time of infringement. Further, claims valid at the time of issuance would become invalid for lack of enablement as the meaning of those claim terms changed. . . . No court has suggested that the meaning of patent claims for validity purposes should be mutable over time in this way, and the debilitating uncertainty associated with these changes counsels against adopting it.<sup>184</sup>

*Schering* potentially suffered from just these sort of problems: the changing understanding of interferons would have meant that “IFN- $\alpha$ -1” took on different meanings for different defendants or that the patent could have withstood validity challenges on some days but not others.<sup>185</sup> Cases like *Schering* ultimately show that science runs the risk of running away with the enablement inquiry.

In this sense, the enablement doctrine, despite its nominal concern with whether others can actually work the patented invention, fails to properly account for a real, scientific basis that the invention actually works. Far from being a substantive test of the workability of the patentee's disclosure, enablement may, like patentable subject matter, “depend simply on the draftsman's art.”<sup>186</sup> The onus therefore lies on patent attorneys to draft reasonable descriptions of plausible

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183. See Lemley, *supra* note 13, at 115–16.

184. *Id.* at 116.

185. Regarding the former contention, that IFN- $\alpha$ -1 could have taken on different meanings for different defendants, this was, in substance, Schering's infringement argument at trial: that IFN- $\alpha$ -1 covered a “mature” version of the protein, one made by the defendant, Amgen. Concerning the second contention, that scientifically evolving claim terms both wax and wane a patent's validity, this is arguably why Schering was quick to drop its case after it lost its claim-construction ruling—an effort to preserve its patent's validity. See *D. De. Grants Judgment to Amgen So Opponent Can Appeal Markman Ruling*, ANDREWS DEL. CORP. LITIG. REP., Apr. 5, 1999, at 9 (discussing Schering's strategy and the district court's dismissal of Amgen's invalidity counterclaim).

186. *Parker v. Flook*, 437 U.S. 584, 593 (1978).

therapeutic correlations between drugs and diseases, not on clinicians to investigate them. And enablement—the seemingly best outlet for encouraging the reproducibility of patented inventions—does very little work itself.

### B. *The Scope of the Enablement Inquiry*

The enablement doctrine may also discourage reproducibility in patents for doctrinal rather than scientific reasons: the law is unclear how *much* of a patent needs to be reproducible to be enabled. Interpretations of enablement that allow some patent claims to be reproducible—although indifferent to the remainder—invite inventors to draft their patents to cover embodiments of their inventions that simply cannot be reproduced. This is complicated by the Federal Circuit's jurisprudence on just what the enablement doctrine is meant to cover. Although it seems clear that the enablement doctrine operates on patents' claims, rather than some abstract concept of “[the] invention,”<sup>187</sup> the Federal Circuit has been “inconsistent and chaotic” in resolving the scope of the enablement inquiry.<sup>188</sup> In several cases, the court appears to have haphazardly chosen among several irreconcilable alternatives to determine whether, and to what extent, enablement operates on the scope of a patent's claims.<sup>189</sup> In an effort to impart order on the court's jurisprudence, Kevin Emerson Collins has broadly grouped the court's decisions into three doctrines: the full-scope doctrine, the single-embodiment doctrine, and the reasonableness doctrine.<sup>190</sup> Each of these standards has encouraged research reproducibility differently.

The full-scope doctrine requires that a patent's specification enable the full scope of the patent's claims.<sup>191</sup> That is, the patent must enable every potential embodiment of the invention—every way or mechanism it can be achieved—arising from the way the claim is drafted. This has been likened to a commensurability requirement,

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187. See *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1241 (Fed. Cir. 2003) (“Because a patent specification must enable the full scope of a claimed invention, an enablement inquiry typically begins with a construction of the claims.” (citations omitted)); MPEP, *supra* note 163, § 2164.08 (“All questions of enablement are evaluated against the claimed subject matter.”); Jacob S. Sherkow, *The Natural Complexity of Patent Eligibility*, 99 IOWA L. REV. 1137, 1170–71 (2014) (“[T]here is no concept of ‘the invention’ apart from the patent's claims.”).

188. Collins, *supra* note 13, at 1087.

189. See *id.* at 1087–88.

190. *Id.* at 1088–89.

191. *Id.* at 1088.

where the patent's disclosure must be commensurate with the scope of the patent's claims.<sup>192</sup> Under this theory, a patent that discloses anything less than all potential embodiments for its claims is invalid. *Wyeth & Cordis Corp. v. Abbott Laboratories*<sup>193</sup> serves as a prime example of the doctrine at its most forceful. In *Wyeth*, the patentee claimed a method for treating restenosis, the narrowing of blood vessels, using "rapamycin."<sup>194</sup> The parties disputed, however, whether the claims' use of the term "rapamycin" constituted a virtually limitless class of chemicals or a well-defined set of known drugs.<sup>195</sup> When the court chose the former definition, it summarily invalidated the patent for lack of enablement, concluding that "practicing the full scope of the claims would require synthesizing and screening *each* of at least tens of thousands of compounds."<sup>196</sup>

This standard comports well with promoting reproducibility in preclinical research. The full-scope doctrine under *Wyeth* seems to encourage patent applicants to either generate enough robust evidence to prove the veracity of broad claims—perhaps by, indeed, screening tens of thousands of compounds—or by drafting their patents much more narrowly, to be commensurate with the research they can, in fact, perform. In either event, tethering enablement to a full-scope analysis pushes researchers to one of two sides of reproducibility: either better, more detailed preclinical research to include in broad patent applications or narrower claims to fit narrower conclusions.

The single-embodiment doctrine, by contrast, is satisfied when the patent specification enables a person having ordinary skill in the art to create at least a single embodiment of the claimed invention.<sup>197</sup> In *Spectra-Physics, Inc. v. Coherent, Inc.*,<sup>198</sup> the Federal Circuit concluded

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192. See, e.g., *In re Wands*, 858 F.3d 731, 741 (Fed. Cir. 1988) ("[T]he claims must be commensurate with the inventor's contribution."); Collins, *supra* note 13, at 1086 ("More specifically, enablement employs the concept of *commensurability* to restrict claim scope: it mandates that the set of the technologies described by a claim remain commensurate with the set of technologies enabled by the disclosure." (footnote omitted)); Karshtedt, *supra* note 4, at 1534 ("[C]ommensurability between claim scope and disclosure . . . is understood to be a part of the enablement requirement in patent law."); Seymore, *supra* note 29, at 634 ("The test is whether the enablement provided in the disclosure is commensurate in scope with the protection sought by the claims." (footnote omitted)).

193. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380 (Fed. Cir. 2013).

194. *Id.* at 1382.

195. *Id.* at 1384–85.

196. *Id.* at 1385.

197. Collins, *supra* note 13, at 1088.

198. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987).



that the inventor's patent on a gas laser was enabling, even though it failed to disclose one possible method for constructing it.<sup>199</sup> This was "not fatal" to the inventor's patent because in "an art where the results are predictable, e.g., mechanical as opposed to chemical arts, a broad claim can be enabled by disclosure of a single embodiment, and is not invalid for lack of enablement simply because it reads on another embodiment of the invention which is inadequately disclosed."<sup>200</sup> From a reproducibility perspective, this can be problematic. Inventions predicated on single working embodiments are akin to research conclusions based on low sample sizes. There is decreasing certainty that their results are, in fact, more generalizable to a broader population.

Lastly, the reasonableness doctrine attempts to navigate between the first two. There, a patent application satisfies the enablement requirement when there is a "reasonable correlation" between the disclosure and the claims.<sup>201</sup> Practically speaking, patent applicants or litigants have attempted to use this reasonableness doctrine in unpredictable arts where there is a wide disparity between the scope of their claims—broad—and the scope of their disclosure—often narrow. To support this analysis, defenders of the reasonableness doctrine often invoke another of the court's patent doctrines, that of the "pioneering" inventor.<sup>202</sup> Older court cases seem to have given leeway to inventors of pioneering inventions "in exchange for their outsized technological contribution to society."<sup>203</sup> Nonetheless, recent cases have rejected the use of the reasonableness doctrine as the touchstone for enablement.<sup>204</sup>

Although the Federal Circuit's language has recently been more forceful in adopting the full-scope doctrine as the polestar for

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199. *Id.* at 1536–38. The patentee's laser required securing several copper cups to the inside of the laser's discharge tube and disclosed several methods of doing so. It failed to teach one method, however—the patentee's own (and presumably proprietary) "six-stage [TiCuSil] braze cycle." *Id.* at 1531.

200. *Id.* at 1533 (citations omitted).

201. Collins, *supra* note 13, at 1089.

202. *See, e.g.*, *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003) (affirming the invalidation of a patent despite appellant's challenge of the district court's failure to make a finding as to the invention's "pioneer" status); *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) (invalidating the patent application's claims even though "appellants assert that their invention is 'pioneering,' and that this should entitle them to claims of broad scope").

203. Brian J. Love, *Interring the Pioneer Invention Doctrine*, 90 N.C. L. REV. 379, 382 (2012).

204. *See supra* note 202.

enablement,<sup>205</sup> it has yet to overrule either the single-embodiment or reasonableness doctrines. Confusion regarding the existence of these alternative doctrines and when they might be applicable continues to persist in the court's own full-scope cases.<sup>206</sup> And scholars have criticized the rule as “unworkable.”<sup>207</sup> But this only further demonstrates the disconnect between encouraging thorough, painstaking clinical research and enablement's lesser requirements for patentability. Concerning the latter, Bernard Chao has described the arguable inequities in requiring perfect reproducibility in patent applications: “There is always an unforeseen embodiment that falls within a claim. In many cases, that embodiment will not be enabled. But a claim should not be invalidated simply because the inventor did not foresee every embodiment that may eventually fall within its scope.”<sup>208</sup>

### C. *The Enablement Doctrine's Relationship with Utility*

Lastly, the enablement doctrine may also encourage irreproducible patent claims in the way it is assessed alongside another doctrine: utility. Indeed, in some circumstances, enablement and utility are often confused. This is problematic because the heart of the utility inquiry asks only whether an invention is theoretically *possible*, and not whether, on the whole, it is consistently *reproducible*. A merging of the two doctrines—as a few courts have done—allows patentees to claim inventions that are largely irreproducible but nonetheless possible.

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205. See, e.g., *Promega Corp. v. Life Techs. Corp.*, 773 F.3d 1338, 1349 (Fed. Cir. 2014) (“As the extensive evidence here demonstrates, undue experimentation would have been required in order to enable the full scope of coverage sought by Promega—the successful co-amplification of potentially thousands of unrecited STR loci combinations.”); *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385 (Fed. Cir. 2013) (“[W]e find no genuine dispute that practicing the full scope of the claims would require more than routine experimentation . . . .”); *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012) (“Hitachi has shown with clear and convincing evidence that one skilled in the art could not have taken the disclosure in the specification regarding ‘change in the resistance by at least 10% at room temperature’ and achieved a change in resistance in the full scope of that term without undue experimentation.” (quoting U.S. Patent No. 5,629,922 col. 8 ll. 50–54 (filed Mar. 21, 1995))).

206. See, e.g., *Wyeth*, 720 F.3d at 1386 (“Even ‘a considerable amount of experimentation is permissible,’ as long as it is ‘merely routine’ or the specification ‘provides a reasonable amount of guidance’ regarding the direction of experimentation.” (quoting *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360–61 (Fed. Cir. 1998))); *MagSil*, 687 F.3d at 1381 (“[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.” (alteration in original) (quoting *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970))).

207. Chao, *supra* note 14, at 1378.

208. *Id.* (citations omitted).

Utility arises from § 101 of the patent statute, which only allows patents on “new and useful” inventions.<sup>209</sup> This has long been “assumed to be a ‘low bar’ to patentability or a ‘nonexistent’ patentability requirement.”<sup>210</sup> It demands only that the patented invention have *some* beneficial use to the public and that the patent itself “be capable of achieving the [invention’s] intended result.”<sup>211</sup> Practically, these requirements set such low thresholds as to be overcome for almost all inventions except the fantastical: perpetual motion machines,<sup>212</sup> processes for cold fusion,<sup>213</sup> and elixirs of eternal youth,<sup>214</sup> for example. By contrast, enablement’s more robust standard requires that a patent actually teach persons having ordinary skill in the patent’s art “to make and use” the invention.<sup>215</sup>

Despite this difference, some courts have confusingly merged the two doctrines. In classic enablement cases, courts have rejected patent applications because they simply do not contain *enough* information to allow a person having ordinary skill in the art to make and use the invention. In *Liebel-Flarsheim Co. v. Medrad, Inc.*,<sup>216</sup> the Federal Circuit concluded that Liebel-Flarsheim’s patent covering a syringe lacked enablement “because the specification [did] not describe a jacketless injector,” a required element of the patent’s claims.<sup>217</sup> The court’s opinion intimated that, had the specification described jacketless injectors *at all*, it would have upheld Liebel-Flarsheim’s patent.<sup>218</sup>

In other cases, however, enablement does not rise or fall on merely the *quantity* of information provided in the specification, but its *quality*.

209. 35 U.S.C. § 101 (2012).

210. Sean B. Seymore, *Making Patents Useful*, 98 MINN. L. REV. 1046, 1049 (2014) (citations omitted).

211. *Id.* at 1066.

212. *Newman v. Quigg*, 877 F.2d 1575, 1577, 1582 (Fed. Cir. 1989).

213. *In re Swartz*, 232 F.3d 862, 863–64 (Fed. Cir. 2000).

214. *In re Eltgroth*, 419 F.2d 918, 922 (C.C.P.A. 1970).

215. 35 U.S.C. § 112(a) (2012).

216. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371 (Fed. Cir. 2007).

217. *Id.* at 1375, 1378.

218. *See id.* at 1378–80. The court noted:

The district court reasoned that the claims were invalid for lack of written description because the specification does not describe a jacketless injector. The court noted that the written description of the invention is directed to the improvement of ‘loading and unloading a syringe given the constraints presented by the pressure jacket.’ . . . The court further found that no prototypes of a jacketless injector had been made or described at the time of filing . . . (citation omitted in original).

*Id.* at 1375.

When the supporting information in the specification gives the patent examiner or the court some doubt that the invention will operate as described, the assessor will often conclude that the patent or patent application lacks enablement because the invention—even if it is physically reduced to practice—will not work as advertised.<sup>219</sup> In other words, the patent disclosure, on its face, does not allow a person having ordinary skill in the art to *use* the invention.

This is precisely what happened in *Process Control Corp. v. HydReclaim Corp.*<sup>220</sup> In *Process Control*, the patentee claimed a method of using a gravimetric blender, a machine important in plastic injection molding.<sup>221</sup> The patent's claims required the blender to perform certain calculations when feeding its grist to a later machine, a hopper.<sup>222</sup> Those calculations commanded the blender to determine a “material processing rate” by adding together the processing rate of the material *to* the hopper with the processing rate of material coming *from* the hopper.<sup>223</sup> During claim construction, however, the district court determined that the patent's use of the term “material processing rate” was no different from the processing rate of material *to* the hopper.<sup>224</sup> This presented sincere problems in math; the patent required the blender to perform a calculation,  $A = A + B$ , that was, in some instances, mathematically impossible.<sup>225</sup> The patent's inoperability therefore rendered the patent invalid because it created “a nonsensical method of operation,” one which “fail[ed] to comply

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219. See, e.g., *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1382 (Fed. Cir. 2012) (“The specification containing these broad claims, however, does not contain sufficient disclosure to present even a remote possibility that an ordinarily skilled artisan could have achieved the modern dimensions of this art.”); *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1325 (Fed. Cir. 2009) (“[W]ith regard to studies cited in the specification showing galantamine's ability to reverse scopolamine-induced amnesia in normal rats . . . [n]othing in this teaching leads to an expectation of utility against Alzheimer's disease.” (second alteration in original) (citation omitted)); *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1355 (Fed. Cir. 1999) (“The district court concluded that “[i]f “discharge rate” is construed as Process Control asserts [*i.e.*, the same as the first occurrence of discharge rate], this specification would be nonsensical.” (alteration in original) (quoting District Court order)).

220. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350 (Fed. Cir. 1999).

221. *Id.* at 1352–54.

222. *Id.*

223. *Id.* at 1354.

224. *Id.* at 1357.

225. *Id.* at 1359 (“In other words, clause [d] requires determining a quantity from the sum of that exact same quantity and something else, or symbolically,  $A = A + B$ , which is impossible, where, as here,  $B$  is not equal to zero.” (brackets in original)).

with the utility *and* enablement requirements of 35 U.S.C. §§ 101 and 112.”<sup>226</sup>

But most patents with inoperability concerns do not fail because their inventions violate fundamental laws of physics or math. Rather, putatively inoperable patents often fail simply because the specification fostered doubt as to the invention’s ultimate success.<sup>227</sup> This was the view of inoperability taken by the court in *Eli Lilly*, where the court struggled to make sense of the dearth of evidence that atomoxetine could be used to treat ADHD.<sup>228</sup> There, the court referred to this intersection between enablement and utility as “enablement/utility.”<sup>229</sup> As evidence for upholding the patent on these “enablement/utility” grounds, the court proffered both evidence from the patent’s specification as well as general scientific principles.<sup>230</sup>

It is this view of enablement—or more precisely, equating enablement to inoperability in cases like *Eli Lilly*—that wrongly conflates the two doctrines. Viewed broadly, the utility requirement is simply concerned with whether the patent describes *a* use for its claimed invention—any use will do. If the patent is silent or hopelessly vague about the invention’s potential uses, or truly impossible as in *Process Control*, then it is fair to say that the patent does not describe

226. *Id.* (emphasis added).

227. See Karshtedt, *supra* note 4, at 111–13 (likening this aspect of inoperability to “unpredictable and unreliable” results (quoting *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988))); Seymore, *supra* note 210, at 1091. Seymore notes:

This last point reveals the paradoxical nature of the modern utility requirement as it relates to disclosure. An applicant can assuredly disclose an invention which enables a PHOSITA to make and use the invention (like a chemical compound), but can nevertheless fail to meet the § 101 utility threshold because the subject matter is deemed to be a “mere research proposal” or “simply an object of research.”

*Id.* (quoting *In re ’318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009)).

228. See *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917, 923–24 (Fed. Cir. 2011); *supra* notes 152–61 and accompanying text.

229. *Eli Lilly & Co.*, 435 F. App’x at 923.

230. *Id.* at 925 (“The district court’s statement that ‘there was no credible disclosure of utility to begin with’ does not comport with the specification’s extensive disclosure of utility.” (quoting *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 731 F. Supp. 2d 348, 386 n.18 (2010))); *id.* at 926. The court noted:

In the case of atomoxetine, however, the norepinephrine relationship was known, safety for antidepressant activity had been established, the specification contained a full description of the utility, experimental verification had been obtained before the patent was granted, and the examiner had not requested additional information. There was no evidence that the disclosure is “on its face, contrary to generally accepted scientific principles.”

*Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971)).

even a single use for its claimed invention.<sup>231</sup> By contrast, a patent should not fail for lack of utility if the uses it describes are plausible but ultimately specious. Determining whether such uses are, in fact, specious likely turns on whether someone can bring them into reality. That inquiry—whether a person having ordinary skill in the art can make or use the invention—is one for the doctrine of enablement, not utility.

This distinction is critically important for unpredictable sciences and industries where trial and error is the order of the day.<sup>232</sup> Nonetheless, the Federal Circuit has been clear that “[I]lack of enablement and absence of utility are closely related grounds.”<sup>233</sup> Although an inventor’s “misconceptions about scientific principles” will not often invalidate the patent,<sup>234</sup> this joining of enablement and utility, even for well-supported but doubtful claims, remains.

### III. IRREPRODUCIBILITY IN DRUG PATENTS

#### A. *Incentives for Irreproducible Drug Patents*

Despite enablement’s concern with disclosure and the workability of inventions, reproducibility seems to play little role in patent law. Patented inventions grounded in irreproducible science are not stripped of their patents as a matter of course. The most relevant doctrine, enablement, appears ill-suited to take irreproducibility into account: it is unclear whether any postapplication evidence can be introduced to invalidate patents based on irreproducible data, let alone general scientific advances that call into question prior assumptions about a particular field.<sup>235</sup> Enablement’s relationship with the scope of patents’ claims—and, consequently, which aspects of patents may or may not be irreproducible—remains stubbornly unsettled.<sup>236</sup> Moreover, the doctrine remains confusingly mixed up with operability,

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231. Seymore, *Making Patents Useful*, *supra* note 210, at 1087–91 (discussing *Brenner v. Manson*, 383 U.S. 519 (1965)).

232. *See Karshedt*, *supra* note 4, at 120–27 (describing this in the context of biotechnology process claims).

233. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999) (citation omitted).

234. *Id.* at 1359.

235. *See supra* Part II.A.

236. *See supra* Part II.B.

a single concern in the broader concept of irreproducibility.<sup>237</sup> In this sense, even though irreproducible patents can be thought of as *disenabling*, they remain entitled, as with other patents, to an ongoing presumption of validity.<sup>238</sup>

This disconnect between reproducibility and enablement becomes particularly problematic in the case of patented drugs. The lifecycle of the drug-approval process—discovery, preclinical development, an Investigational New Drug Application with the FDA, three phases of clinical trials, and, finally, approval—counsels patenting early on, when very little data concerning drugs' efficacy in their target populations is available.<sup>239</sup> Indeed, because of the “statutory bars”—statutory limits on how long inventors have to file patent applications with the PTO after initially disclosing their inventions—“the patent laws actually penalize inventors who fail to file promptly.”<sup>240</sup>

To avoid this, drug developers often rely on early preclinical studies to bolster their patents.<sup>241</sup> By design, these studies often have small sample sizes; employ little statistical power; and, of course, suffer from conflicts of interest between industrial researchers and their

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237. See *supra* Part II.C (discussing the differences among empirical, statistical, and computational reproducibility).

238. See 35 U.S.C. § 282 (2012) (“A patent shall be presumed valid.”); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 923–26 (Fed. Cir. 2011) (concluding that Eli Lilly's patent satisfied the enablement requirement even though the defendant raised doubts about the studies included in the patent's specification).

239. *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1536 (Fed. Cir. 1995) (en banc) (Newman, J., concurring) (per curiam), *rev'd on other grounds*, 520 U.S. 17 (1997) (“[T]he patent law places strong pressure on filing the patent application early in the development of the technology, often before the commercial embodiment is developed or all of the boundaries fully explored.”); Eisenberg, *supra* note 24, at 348 (“Basic ‘composition of matter’ patents on drugs are typically issued in the early stages of product development, before the effects of these molecules have been tested in clinical trials.”); Seymore, *supra* note 143, at 161–62 (quoting *Hilton Davis* and discussing this in the context of pharmaceutical development); see also Cotropia, *supra* note 20, at 93–96 (describing the negatives of early patent filing).

240. Seymore, *supra* note 143, at 162.

241. See Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 539 (2009) (“Pharmaceutical patents are typically filed when drugs are in early preclinical research . . .”).

employers<sup>242</sup>—all hallmarks of irreproducibility.<sup>243</sup> Nonetheless, patent applications rooted in suspect data from preclinical trials do not suffer at the PTO. Rather, the Manual of Patent Examining Procedure requires only a “reasonable correlation” between a drug and its asserted benefit,<sup>244</sup> a standard that can be met with mere animal testing or *in vitro* analyses.<sup>245</sup> The PTO even appears to acknowledge the deficiency of this approach, reminding its examiners that “[t]he applicant *does not* have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty.”<sup>246</sup>

The early, easy patenting of drugs encourages patent applicants to adopt several troublesome strategies at the PTO. Patentees of new drugs, already encouraged to claim broadly,<sup>247</sup> often draft their claims as directed to methods of treating broader classifications of diseases than any preclinical data warrants.<sup>248</sup> U.S. Patent No. 8,652,776, for

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242. See, e.g., Katherine S. Button et al., *Power Failure: Why Small Sample Size Undermines the Reliability of Neuroscience*, 14 NATURE REV.: NEUROSCIENCE 365, 373 (2013) (describing these factors as “the root of the recent replication failures in the preclinical literature”); Ioannidis, *Research Findings*, *supra* note 9, at 697–98 (same). See generally David M. Katz et al., *Preclinical Research in Rett Syndrome: Setting the Foundation for Translational Success*, 5 DISEASE MODELS & MECHANISMS 733 (2012) (attempting to establish best practices for preclinical research for treatments of Rett syndrome); Iurii Koboziev, Fridrik Karlsson, Songlin Zhang & Matthew B. Grisham, *Pharmacological Intervention Studies Using Mouse Models of the Inflammatory Bowel Diseases: Translating Preclinical Data into New Drug Therapies*, 17 INFLAMMATORY BOWEL DISEASES 1229 (2011) (criticizing preclinical studies of inflammatory bowel disease in mice); Emily Sena, H. Bart van der Worp, David Howells & Malcolm Macleod, *How Can We Improve the Pre-Clinical Development of Drugs for Stroke?*, 30 TRENDS NEUROSCIENCE 433 (2007) (exploring the failures of preclinical studies in drugs for stroke); Hanna M. Vesterinen et al., *Improving the Translational Hit of Experimental Treatments in Multiple Sclerosis*, 16 MULTIPLE SCLEROSIS 1044 (2010) (criticizing preclinical research for multiple sclerosis treatments on various grounds).

243. Ioannidis, *Research Findings*, *supra* note 9, at 697–98.

244. MPEP, *supra* note 163, § 2107.03.

245. *Id.*

246. *Id.* (emphasis added).

247. Chao, *supra* note 14, at 1366–67 (“Patent attorneys draft claims as broadly as they can. In fact, they often deliberately seek overly broad claims in the hope that the patent office will accept them.”).

248. See Budish et al., *supra* note 8, at 2077 (“[T]he drug Tamoxifen was FDA approved for several cancer indications while on-patent; later, a publicly funded clinical trial supported the 1998 FDA approval of Tamoxifen as a chemoprevention agent, preventing breast cancer incidence in high-risk groups.”); Feldman, *supra* note 13, at 13–15 (describing this in the context of antibody therapeutics); Eileen M. Kane, *Patent-Mediated Standards in Genetic Testing*, 2008 UTAH L. REV. 835, 859 (“[T]he establishment of new mutations that are associated with clinical risk might rise to the level of ‘undue experimentation’ that would indicate a patent claim that is potentially broader than its disclosure.”); Price, *supra* note 77, at 445 (weighing similar incentives in the



example, generally claims a method of using iloperidone to treat “one or more symptoms of a psychotic disorder”—a virtually limitless category—even though the preclinical studies referenced by the patent refer almost exclusively to schizophrenia.<sup>249</sup> Similarly, to the extent that a drug has multiple forms, patentees are encouraged to base their claims on the broadest genus of the drug, even if there is little data to support their claims.<sup>250</sup> Patentees for new drugs also have little incentive to include in their applications a full description of the statistical methods used in any of their preclinical research. Rather, patentees are encouraged to say little about the methodology of any supporting studies and then wait for an examiner’s response.<sup>251</sup> In that vein, the Federal Circuit’s conflicting decisions in *In re ’318 Patent* and *Eli Lilly* suggest that examiners’ objections to preclinical studies—if any—are of much greater consequence than whether the studies are, in any sense, reproducible.<sup>252</sup> Lastly, patentees may also be encouraged to draft ambiguous claims in the hope of retaining textual flexibility as developmental research on the studied drug progresses.<sup>253</sup> Claiming a method of treatment with keen specificity, for example, may hinder a patent holder’s later efforts to expand the definition of that treatment in future infringement suits.<sup>254</sup> In these ways, the incentives giving rise to irreproducible drug patents are the product of numerous interrelated legal regimes: drug-development-patent policy, patent-examination procedure, FDA policy, and the economic realities of preclinical testing.

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context of diagnostic algorithms); Roin, *supra* note 241, at 522–26 (describing this practice’s effect on patentability); Sean B. Seymore, *Patently Impossible*, 64 VAND. L. REV. 1489, 1517–23 (discussing the history of patents on cancer treatments).

249. U.S. Patent No. 8,652,776 col. 15 ll. 60–61 (filed Sept. 10, 2008).

250. Seymore, *supra* note 143, at 145–46 (“A generic claim uses structural formulas or functional language to cover embodiments that share a common attribute . . . and affords the broadest claim scope under the patent laws. . . . Indeed, a single generic claim can easily encompass millions, billions, or novemdecillions of compounds.” (citations omitted)). *But see* *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385 (Fed. Cir. 2013) (rejecting this approach).

251. Lemley, *supra* note 13, at 117 (discussing the patentee’s strategy of “control[ling] when the patent issues and with what claims” in *Chiron Corp. v. Genentech, Inc.*, 266 F. Supp. 2d 1172 (E.D. Cal. 2002)).

252. *Compare In re ’318 Patent Infringement Litigation*, 583 F.3d 1317, 1327 (Fed. Cir. 2009) (noting the examiner’s objections to future evidence), *with Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917, 925–26 (Fed. Cir. 2011) (noting the absence of objections by the examiner).

253. *See* Chao, *supra* note 14, at 1372–75 (discussing the incentives behind unclear claiming).

254. *See* Collins, *supra* note 13, at 1090–92 (discussing the expansion of claim language with time to cover after-arising technology).

*B. Examples of Irreproducible Drug Patents*

The irreproducibility of drug patents does not occur only at the margins. Numerous blockbuster drugs are protected by patents grounded in some form of irreproducible data. Much in the same way that irreproducibility is a varied concept,<sup>255</sup> the character of irreproducibility in drug patents is similarly varied: it can manifest in patents based on contradicted preclinical or clinical trials, patents based on irreproducible effects, patents covering a broader indication or target population than warranted, and patents based on such a small effect as to make their veracity doubtful. Prempro, Xigris, Plavix, and Avastin each respectively demonstrate these deficiencies.

1. *Prempro: Contradicted Data.* Perhaps the most extreme example of patents grounded in later-contradicted data concerns those related to postmenopausal hormone-replacement therapy. Menopause—the cessation of ovulation in women, most often due to age—has long been thought to bring with it several ailments, including bone loss, cardiovascular disease, and ovarian cancer.<sup>256</sup> Clinicians attribute the onset of these illnesses, at least in part, to the decrease in hormone production following menopause.<sup>257</sup> Hormone-replacement therapy (HRT)—small doses of hormones intended to mimic a premenopausal state—was consequently viewed as a logical treatment.<sup>258</sup>

Beginning in the 1980s, numerous companies began to manufacture, market, and patent various types of HRTs as treatments to ameliorate menopause-related illnesses.<sup>259</sup> Wyeth Pharmaceuticals, the largest HRT manufacturer,<sup>260</sup> sold several different therapies: Premarin, Prempro, and Premphase.<sup>261</sup> Unsurprisingly, Wyeth also

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255. For the differences between empirical, statistical, and computational reproducibility, see *supra* Part I.A.

256. Millrood, *supra* note 101, at 42 (discussing Women's Health Initiative Study, *supra* note 101, at 321).

257. *Id.* (citing Bernardine Healy, *The Mysteries of Menopause*, U.S. NEWS & WORLD REP., Nov. 18, 2002, at 39, 41).

258. *Id.* at 43 (examining the history of hormone therapy).

259. *See id.* at 42 ("In all, about 10 companies manufacture the more than two dozen hormone therapy products currently available.").

260. *See In re Pfizer, Inc.*, 135 F.T.C. 608, 782 (2003) (noting that, prior to acquisition, Wyeth was the primary HRT manufacturer).

261. *See* Ganesa Wegienka, Suzanne Havstad & Jennifer L. Kelsey, *Menopausal Hormone Therapy in a Health Maintenance Organization Before and After Women's Health Initiative Hormone Trials Termination*, 15 J. WOMEN'S HEALTH 369, 370–71 (2006).

sought to protect each of these drugs with various patents. U.S. Patent No. RE36,247, for example, covered Prempro,<sup>262</sup> which claimed “[a] method of hormonally treating menopausal or post-menopausal disorders in a woman,”<sup>263</sup> including “dosages and duration of treatment . . . sufficient to prevent or retard changes in blood lipids which might otherwise predispose the woman to cardiovascular disease.”<sup>264</sup> Yet the basis for the patent’s cardiovascular claims lay in a single preclinical study, a study replete with the indicia of irreproducibility: a small sample size of only thirty subjects; an opaque and flexible design that did not clearly state the measurements for a decrease in risk of cardiovascular disease; a significant potential for conflict of interest, given the inventors’ original assignment of their patent to an investment firm; and a high quotient of competitive popularity with other treatments.<sup>265</sup> Despite these concerns, Prempro’s annual sales topped \$733 million by 2001,<sup>266</sup> its success much indebted to Wyeth’s aggressive marketing of the drug’s cardiovascular benefit.<sup>267</sup>

The rapid rise of HRTs—and questions concerning their actual benefits—led the NIH to support large-scale randomized trials of HRTs.<sup>268</sup> One such trial, a 2002 study of various HRTs, called the Women’s Health Initiative Study, came to the opposite conclusion of Prempro’s patent and an earlier, major 1991 observational trial.<sup>269</sup> Rather than *preventing* cardiovascular disease in menopausal women, HRTs, including Prempro, “significantly *increased* the relative risk of coronary events by 29% among postmenopausal women.”<sup>270</sup> A further follow-up randomized trial, the Heart and Estrogen–Progestin Replacement Study, came to a similar damning conclusion.<sup>271</sup> The

262. See CTR. FOR DRUG EVALUATION & RESEARCH, TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53 FOR NDA 20-527, at 2 (Apr. 13, 2000), [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2003/20-527S017\\_Prempro%20&%20Premphase\\_AdminCorres\\_P1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/20-527S017_Prempro%20&%20Premphase_AdminCorres_P1.pdf) [<https://perma.cc/W6B4-FF8W>] [hereinafter PATENT INFORMATION].

263. U.S. Patent No. Re. 36,247 col. 10 ll. 22–23 (filed Oct. 13, 1995).

264. *Id.* col. 16 ll. 7–9.

265. See *id.* col. 7 l. 57–col. 9 l. 17 (describing this study and its follow-up).

266. Millrood, *supra* note 101, at 42 n.3.

267. See *id.* at 43 (describing Wyeth’s marketing of its drugs).

268. *E.g.*, Women’s Health Initiative Study, *supra* note 101.

269. See Ioannidis, *Contradicted Effects*, *supra* note 9, at 223 (discussing the Women’s Health Initiative Study, *supra* note 101, and the Nurses’ Health Study, *supra* note 100).

270. *Id.*; see also Women’s Health Initiative Study, *supra* note 101, at 321.

271. Ioannidis, *Contradicted Effects*, *supra* note 9, at 223 (discussing Stephen Hulley et al., *Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease In Postmenopausal Women*, 280 J. AM. MED. ASS’N 605, 605–13 (1998)).

results of these studies spawned countless lawsuits against Wyeth and led, ultimately, to Wyeth's successor, Pfizer, paying \$896 million in settlements.<sup>272</sup>

The products-liability issues aside, this turn of events would seem to suggest that Prempro's patent was never enabling in the first instance. The patent's claims that certain doses of progestogen and estrogen could *prevent* cardiovascular disease were simply incorrect.<sup>273</sup> In that sense, a person having ordinary skill in the medical art could simply not "make and use" the invention.<sup>274</sup> This conclusion seems to hold despite the ambiguities in the enablement doctrine concerning its scope: the patent's claims lacked a corresponding enabling disclosure no matter whether the enablement doctrine encompassed a full-scope, single-embodiment, or reasonableness analysis.<sup>275</sup> Furthermore, whatever the difficulties surrounding enablement's overlap with inoperability, they appear neatly resolved when considering Prempro's patent: because the patented method produces the *opposite* effect of what it intended, the claims ultimately required an impossible, "nonsensical method of operation."<sup>276</sup>

Yet, enablement's focus on *pre*application evidence, even in the face of contradictory scientific advances,<sup>277</sup> casts this analysis into doubt. It is unclear whether litigants seeking to invalidate Prempro's patent could have introduced such evidence. A recent district court lawsuit, *Gilead Sciences, Inc. v. Mylan Inc.*,<sup>278</sup> suggests otherwise.<sup>279</sup> In *Gilead*, the plaintiffs sought discovery of the defendants' Abbreviated New Drug Application with the FDA, to combat the defendants' arguments concerning the asserted patent's lack of enablement.<sup>280</sup> The district court refused on the grounds that "everything that the Plaintiffs would need to defend against a claim of invalidity through enablement

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272. Jef Feeley, *Pfizer Paid \$896 Million in Prempro Settlements*, BLOOMBERG (June 19, 2012), <http://www.bloomberg.com/news/articles/2012-06-19/pfizer-paid-896-million-in-prempro-accords-filing-shows-1> [<https://perma.cc/Z5KP-RF2B>].

273. See U.S. Patent No. Re. 36,247 col. 16 ll. 7–9 (filed Oct. 13, 1995).

274. See 35 U.S.C. § 112(a) (2012).

275. See Collins, *supra* note 13, at 1088 (describing the differences in these doctrines).

276. See *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1359 (Fed. Cir. 1999); see also *supra* Part II.C (discussing the difficulties concerning enablement's relationship with inoperability).

277. See *supra* Part II.A.

278. *Gilead Scis., Inc. v. Mylan, Inc.*, No. 1:14-cv-99, 2015 WL 4042161 (N.D. W. Va. July 1, 2015).

279. *Id.* at \*1–2.

280. *Id.*

theory [was] within the four corners of the Plaintiffs' own patent."<sup>281</sup> This suggests, too, that everything the defendants needed to make their claim of invalidity was also limited to the four corners of the patent. Ultimately, Prempro's patent was never litigated to judgment in federal court,<sup>282</sup> and it quietly expired on May 2, 2006.<sup>283</sup>

2. *Xigris: Irreproducible Effects.* Not all irreproducible patents have contradictory indications. Others are irreproducible because follow-on trials are unable to reproduce the effects seen in preclinical or early-stage clinical trials; the underlying data is literally *irreproducible*. Xigris, a drug approved by the FDA in 2001 to treat sepsis<sup>284</sup> and voluntarily withdrawn by its manufacturer Eli Lilly in 2011,<sup>285</sup> serves as a prime example.

Sepsis is a general inflammatory response to an infection.<sup>286</sup> In severe cases, sepsis can cause the coagulation of blood and the creation of circulating blood clots.<sup>287</sup> These symptoms are often worse than the initial infection: coagulation and clotting from sepsis is the tenth leading cause of death in the United States, where it kills over a million people a year, or 6 percent of all recorded deaths.<sup>288</sup> The inflammation pathway giving rise to sepsis is complex—isolating the proteins responsible still baffles scientists<sup>289</sup>—but one protein involved,

281. *Id.* at \*2.

282. Intermediary owners of the Prempro patent filed only one lawsuit against two other HRT manufacturers, Novo Nordisk and Pharmacia & Upjohn, in the U.S. District Court for the District of New Jersey. That case settled by consent decree. Consent Decree and Order, *Am. Home Prods. Corp. v. Novo Nordisk Pharm., Inc.*, No. 3:99-cv-3162 (D.N.J.) (signed June 23, 2000), ECF No. 24.

283. See PATENT INFORMATION, *supra* note 262, at 2.

284. See FDA, FDA CLINICAL REVIEW DROTRECOGIN ALFA (ACTIVATED) 1, 8 (Nov. 21, 2001), <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113438.pdf> [<https://perma.cc/S6B4-HCKS>] [hereinafter FDA, DROTRECOGIN ALFA].

285. Press Release, Eli Lilly & Co., Lilly Announces Withdrawal of Xigris® Following Recent Clinical Trial Results (Oct. 25, 2011), <https://investor.lilly.com/releasedetail.cfm?releaseid=617602> [<https://perma.cc/L5CX-6CLM>].

286. FDA, DROTRECOGIN ALFA, *supra* note 284, at 9.

287. *Id.*

288. See Alexander Melamed & Frank J. Sorvillo, *The Burden of Sepsis-Associated Mortality in the United States from 1999 to 2005: An Analysis of Multiple-Cause-Of-Death Data*, 13 CRITICAL CARE, No. 1, 2009, at 1.

289. Charalampos Pierrakos & Jean-Louis Vincent, *Sepsis Biomarkers: A Review*, 14 CRITICAL CARE, No. 15, 2010, at 1.

activated protein C (APC), had long been hypothesized to play a role in inhibiting fatal coagulation and clotting.<sup>290</sup>

In 2001, Eli Lilly received FDA approval for a recombinant version of APC, marketed as Xigris, for the treatment of severe sepsis.<sup>291</sup> Eli Lilly also obtained a number of patents claiming the use of APC to treat sepsis, including U.S. Patent Nos. 6,344,197 and 6,489,296.<sup>292</sup> But, having yet to complete its clinical trials for APC by the time the patents were filed, both patents were based on early preclinical data. The '197 patent, for example, claims "[a] method of treating a patient suffering from sepsis" by administering a combination of APC and another protein, bactericidal/permeability-increasing protein, based on the patient's body weight.<sup>293</sup> Given the patent's description of the invention, this sounds like a promising treatment. Yet, the basis for the '197 patent's claims rests only on the thinnest reed of data: a preclinical, prophylactic trial in baboons—and even then, only ten baboons.<sup>294</sup> As for a human trial, the patent only proposes a protocol for conducting one.<sup>295</sup>

The '296 patent similarly claims "[a] method of reducing mortality in a human patient with severe sepsis which comprises administering a dose of human activated Protein C to the patient as a continuous infusion."<sup>296</sup> But unlike the '197 patent, the basis for the '296 patent's claims seems more robust: an actual human-subject clinical trial that measured the mortality rate of sepsis-suffering subjects receiving APC against those who did not.<sup>297</sup> Although the sample size of the trial was small—only seventy-two subjects total—the results seemed strong: sepsis patients receiving APC died at almost half the rate of the patients who did not receive APC after twenty-eight days.<sup>298</sup> In comparison to the '197 patent's data, the results predicated the '296 patent seemed promising. And that promise—as well as the '197 and '296 patents, among others—led Eli Lilly to aggressively market Xigris. Eventually, the Centers for Medicare and Medicaid Services accepted

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290. FDA, DROTRECOGIN ALFA, *supra* note 284, at 9.

291. *See id.* at 1, 8.

292. U.S. Patent No. 6,489,296 (filed May 10, 2000); U.S. Patent No. 6,344,197 (filed Oct. 22, 1999).

293. '197 Patent col. 10 ll. 39–43.

294. *Id.* col. 2 ll. 19–36.

295. *Id.* col. 10 ll. 6–37.

296. '296 Patent col. 15 ll. 14–17.

297. *Id.* col. 13 l. 48–col. 14 l. 49.

298. *Id.* col. 13 ll. 54–56, col. 14 ll. 4–10.

Xigris as “the first and only medical product to be granted new technology status for the substantial improvement in . . . patients with life-threatening severe sepsis.”<sup>299</sup> As a result, Xigris garnered Eli Lilly over \$100 million per year in sales.<sup>300</sup>

This promise was not to last, however. The FDA conditioned its approval of Xigris on a larger follow-up study that enrolled over a thousand patients, rather than mere dozens.<sup>301</sup> That study showed that Xigris did no better than the placebo and “was not beneficial when administered to a population of patients for which it was an approved treatment.”<sup>302</sup> The new study, in other words, failed to reproduce the results of Eli Lilly’s earlier study. Faced with this irreproducible data and physician ire,<sup>303</sup> Eli Lilly withdrew its drug from the FDA’s marketing rolls.<sup>304</sup>

And yet, to date, the Xigris patents live on. Neither the ’197 nor the ’296 patent appear to have been challenged in federal court, by a generic competitor or otherwise. And this remains so despite the patents’ potential invalidity for lack of enablement. The core of both patents’ claims—a method of treating sepsis using APC—could not be reproduced in a large-scale, randomized clinical trial. This does not necessarily make them false. Nor does it mean that yet another trial could not conclude otherwise. But it does suggest that, for a person having ordinary skill in the art to “make and use” APC as a sepsis treatment, many more, and more robust, clinical trials would need to be conducted—a case of “undue experimentation” if there ever was one.<sup>305</sup>

But the complexities in the enablement doctrine itself complicate this analysis. First, given the conflicting data on the efficacy of Xigris,

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299. Judy Stone, *Lilly’s Shocker, or the Post-Marketing Blues*, SCI. AM. GUEST BLOG (Nov. 2, 2011), <http://blogs.scientificamerican.com/guest-blog/lillys-shocker-or-the-post-marketing-blues> [https://perma.cc/4Z2E-P5M6].

300. Antonio Regalado, *To Sell Pricey Drug, Eli Lilly Fuels a Debate over Rationing*, WALL STREET J. (Sept. 18, 2003, 1:26 AM), <http://www.wsj.com/articles/SB106382950695778600> [https://perma.cc/YB9X-CHT9].

301. See Stone, *supra* note 299, at 1–2; see also ELI LILLY & CO., FOLLOW-UP DATA OF PATIENTS TREATED WITH XIGRIS® DROTRECIGIN ALFA (ACTIVATED) IN FRANCE 2 (2009), [http://www.lillytrials.com/nonintstudies/result\\_files/12401.pdf](http://www.lillytrials.com/nonintstudies/result_files/12401.pdf) [https://perma.cc/XSE2-EAMC] (enrolling 1049 patients).

302. V. Marco Ranieri et al., *Drotrecogin Alfa (Activated) in Adults with Septic Shock*, 366 NEW ENG. J. MED. 2055, 2063 (2012).

303. See Regalado, *supra* note 300.

304. Press Release, Eli Lilly & Co., *supra* note 285.

305. See *supra* notes 133–36 and accompanying text.

it is unclear whether the patents are disabling for the entire scope of their claims or just some part of them.<sup>306</sup> Xigris may, in fact, work for some patients in some circumstances (although this is doubtful).<sup>307</sup> In that sense, whether the Xigris patents are enabling turns on resolving the scope of the enablement inquiry. Furthermore, to the degree enablement overlaps with utility in the pharmaceutical context, it is unclear whether the patents truly require a prohibited “nonsensical method of operation,”<sup>308</sup> or whether they merely require an improbable *but plausible* method of operation. Lastly, although the ’197 patent appears to be based on truly paltry data, the ’296 patent is rooted in what appears to be a serious preclinical trial—one later confirmed by a larger clinical trial and only then refuted by an even larger clinical trial. To that end, determining whether postapplication evidence can be introduced to invalidate a patent for lack of enablement does not, in fact, resolve the enablement inquiry.<sup>309</sup> Rather, it also raises questions of which postapplication evidence can be used at all and which is controlling. Therefore, in a greater sense, Xigris demonstrates the disconnect between drug development and patent validity: unlike Xigris, which rose and fell on the strength of the clinical data used to assess it, the Xigris patents appear to rise or fall on resolving the contours of the enablement doctrine.

3. *Plavix: Broader Indication or Target Population than Warranted.* Some pharmaceutical patents are irreproducible not due to the overall truth or falsity of their claims but for reasons having to do with precision: they claim a broader indication or patient population than the underlying data warrants. Plavix, for example, was approved by the FDA to reduce “atherosclerotic events,” that is, heart attacks, strokes, and vascular death, in patients previously diagnosed with atherosclerosis.<sup>310</sup> The drug itself—clopidogrel bisulfate—acts on one

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306. For a discussion of this difficulty in the enablement doctrine, see *supra* Part II.B.

307. See Ranieri et al., *supra* note 302, at 2062 (“The lack of benefit was consistent across predefined subgroups.”).

308. See *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1359 (Fed. Cir. 1999).

309. See *supra* Part II.A.

310. CTR. FOR DRUG EVALUATION & RESEARCH, *Final Printed Labeling*, in CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW, APPROVAL PACKAGE FOR PLAVIX 11, 18 (1997), [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/97/20839\\_Plavix\\_appltr\\_prntlbl\\_medr\\_chemr\\_EA\\_phrmr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20839_Plavix_appltr_prntlbl_medr_chemr_EA_phrmr.pdf) [<https://perma.cc/DCT7-HKSL>]; see CTR. FOR DRUG EVALUATION AND RESEARCH, CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW, PLAVIX 2 (1997), [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/97/20839\\_Plavix\\_clinphmr\\_P1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20839_Plavix_clinphmr_P1.pdf) [<https://perma.cc/2H7M-7325>] [hereinafter FDA, PLAVIX].



particular protein, P2Y<sub>12</sub>, to block its role in platelet aggregation, one of the steps in harmful blood clotting.<sup>311</sup> At its peak in 2011, Plavix generated \$9.3 billion in revenue for Sanofi and Bristol-Myers Squibb, two pharmaceutical giants.<sup>312</sup> And naturally, Sanofi was granted a patent on the method of using Plavix to “prevent[] the occurrence of a secondary ischemic event.”<sup>313</sup>

Prior to Plavix exerting its effect on P2Y<sub>12</sub>, however, it must be metabolized into several intermediary chemicals.<sup>314</sup> But not all patients metabolize Plavix similarly. Rather, up to a quarter of all Plavix patients fail to respond to Plavix due to differences in several genes responsible for drug metabolism.<sup>315</sup> One such gene, *CYP2C19*, plays an outsized role in responsiveness to Plavix.<sup>316</sup> Plavix patients with dysfunctional variants of *CYP2C19* are three-and-a-half times more likely to experience a secondary ischemic event than patients without the variant.<sup>317</sup> In other words, a large subpopulation of Plavix patients is entirely resistant to the treatment.<sup>318</sup> In 2011, an enormous follow-on meta-analysis of 42,000 patients confirmed the importance of these genetic differences,<sup>319</sup> and the FDA later required Sanofi to include this information on Plavix’s label.<sup>320</sup>

311. Rashmi R. Shah & Devron R. Shah, *Personalized Medicine: Is It a Pharmacogenetic Mirage?*, 74 BRIT. J. CLINICAL PHARMACOLOGY 698, 702 (2012).

312. Simon King, *The Best Selling Drugs of All Time; Humira Joins The Elite*, FORBES (Jan. 28, 2013), <http://www.forbes.com/sites/simonking/2013/01/28/the-best-selling-drugs-of-all-time-humira-joins-the-elite> [<https://perma.cc/X9VV-3Z3E>].

313. U.S. Patent No. 5,576,328 col. 6 ll. 60–61 (filed Jan. 31, 1994).

314. Shah & Shah, *supra* note 311, at 702 (“Clopidogrel is pharmacologically inactive and requires activation to its pharmacologically active thiol metabolite that binds irreversibly to the P2Y<sub>12</sub> receptors on platelets.”).

315. See Jean-Sébastien Hulot et al., *Cytochrome P450 2C19 Loss-of-Function Polymorphism Is a Major Determinant of Clopidogrel Responsiveness in Healthy Subjects*, 108 BLOOD 2244, 2244 (2006) (“The pharmacodynamic response to clopidogrel varies widely from subject to subject, and about 25% of patients treated with standard clopidogrel doses display low ex vivo inhibition of ADP-induced platelet aggregation. . . . [C]ertain genetic factors may be involved in this phenomenon.”).

316. *Id.*

317. Shah & Shah, *supra* note 311, at 702–03.

318. See Hulot et al., *supra* note 315, at 2244.

319. See Michael V. Holmes et al., *CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events: A Systematic Review and Meta-analysis*, 306 J. AM. MED. ASS’N 2704, 2704 (2011).

320. *FDA Updates Plavix Label with PGx Data, but Does Not Provide Dosing Recommendations*, GENOMEWEB (June 17, 2009), <https://www.genomeweb.com/dxpgx/fda-updates-plavix-label-pgx-data-does-not-provide-dosing-recommendations> [<https://perma.cc/VF Y4-MYKC>].

But the FDA did not require, or even suggest, that Sanofi correct its underlying patents.<sup>321</sup> To the contrary, Sanofi's Plavix method-of-use patent makes no mention of *CYP2C19* or even the possibility that genetic differences among patients may play a role in its effectiveness.<sup>322</sup> This overly broad view of Plavix's efficacy—one that fails to acknowledge that the treatment will fail in up to a quarter of patients—calls the enablement of the patent into question. The patent's claims, directed to “[a] method for preventing the occurrence of a secondary ischemic event [by] administering to a patient . . . a therapeutically effective amount of [Plavix],”<sup>323</sup> do not limit themselves to patients with functioning metabolisms of Plavix. For patients with such metabolic deficiencies, there is *no* “therapeutically effective amount”<sup>324</sup> of the drug. In terms of enablement, a physician treating a patient with such a deficiency cannot—by virtue of biology—“make [or] use” the patented invention.<sup>325</sup>

But again, whether this invalidates the patent seems to turn less on genetics and more on defining the contours of enablement. To the degree that enablement requires a person having ordinary skill in the art to work every limitation of the patent's claims,<sup>326</sup> it seems clear that the Plavix method-of-use patent is invalid. But for three-quarters of the patient populace, the invention is invaluable, “a drug of ‘major historical significance.’”<sup>327</sup> Under a reasonableness or even a single-embodiment interpretation of enablement,<sup>328</sup> therefore, the Plavix method-of-use patent seems enabling, beyond dispute.

Even with the contours of enablement resolved, there remains the thornier issue of how to treat the scientific advances concerning genotyping and genetic sequencing in relation to an older patent. The Plavix method-of-use patent was filed in 1994,<sup>329</sup> when genetic

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321. For a discussion concerning the FDA's role, or lack thereof, in policing drug patents, see Jacob S. Sherkow, *Administrating Patent Litigation*, 90 WASH. L. REV. 205, 214–16 (2015).

322. See U.S. Patent No. 5,576,328 (filed Jan. 31, 1994).

323. *Id.* col. 6 ll. 60–63.

324. *Id.* col. 6 ll. 62–63.

325. See 35 U.S.C. § 112(a) (2012).

326. See Collins, *supra* note 13, at 1088 & nn.19–21 (describing the full-scope doctrine).

327. Michael O'Riordan, *So Long, Plavix, What a Ride! Clopidogrel Patent Expires*, MEDSCAPE: HEARTWIRE (May 17, 2012), <http://www.medscape.com/viewarticle/764052> [<https://perma.cc/Y6ES-SAT8>].

328. See *supra* notes 197–204 and accompanying text.

329. See U.S. Patent No. 5,576,328 (filed Jan. 31, 1994).

sequencing was in a relative infancy.<sup>330</sup> It was therefore unlikely, if not impossible, for the inventor to have been able to assess genetic differences among potential Plavix patients contributing to the drug's efficacy—or lack thereof. In this sense, fixing the enablement inquiry at the time the patent was filed seems to produce one outcome—validity—whereas future advances produce another—invalidity.<sup>331</sup>

Lastly, the Plavix patent demonstrates just how confusing enablement's entanglement with the inoperability doctrine can be. For normal patients, the invention described in the Plavix patent has a well-defined use—the reduction of secondary ischemic events. But for patients with a *CYP2C19* deficiency, the invention is simply useless—it borders, in the words of the *Process Control* court, on a “nonsensical method of operation.”<sup>332</sup> Although inoperability seems to take hold only when *all* embodiments of a patent invention are facially inoperable, it is unclear how the doctrine works—and how it relates to enablement—where an invention is facially inoperable, but only to some users. Plavix accordingly highlights the difficulties in aligning precision medicine with precision claiming.

4. *Avastin: Small Effect Size.* Yet other drug patents seem likely to be irreproducible due to small effect size—that even assuming a statistically significant difference between the drug and a placebo, the benefit of the drug is so small as to make the result doubtful.<sup>333</sup> This is, in fact, a frequent problem with cancer drugs, where the effect size of overall patient survival is often measured in only one or two months.<sup>334</sup> Such small effects often cast doubt on whether the original clinical trials supporting cancer drugs' approval are reproducible.<sup>335</sup> And they also cast doubt on patent claims predicated on using such drugs to treat cancer.

Avastin—a monoclonal antibody manufactured by Roche—was first approved by the FDA in 2004 to treat metastatic colorectal

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330. See ROBERT COOK-DEEGAN, *THE GENE WARS: SCIENCE, POLITICS, AND THE HUMAN GENOME* 56–77 (1994) (discussing the history of genetic sequencing).

331. See Lemley, *supra* note 13, at 106–07 (discussing fixing the meaning of claim terms, and consequently enablement, at the time the patent was filed).

332. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1359 (Fed. Cir. 1999).

333. See Ioannidis, *Research Findings, supra* note 9, at 697–98 (discussing small effect size and reproducibility).

334. See *supra* notes 112–17 and accompanying text.

335. See Light & Lexchin, *supra* note 9, at h2068 (discussing the incremental benefit of many approved cancer drugs).

cancer.<sup>336</sup> The drug was later proven successful—and approved by the FDA—to treat several other cancers, including lung, kidney, brain, and breast cancer.<sup>337</sup> But its efficacy in treating breast cancer was notoriously small. Tested as a combination therapy with another breast cancer drug, paclitaxel—a typical procedure for cancer clinical trials—Avastin improved overall patient survival by a mere 1.7 months.<sup>338</sup> Nonetheless, the FDA approved Avastin for metastatic breast cancer in 2008, although on the condition that Roche conduct two additional follow-on trials.<sup>339</sup>

This insignificant increase in overall survival led several clinicians to question the reproducibility of the drug's efficacy in treating breast cancer. Immediately following approval, the *New York Times* ran a front-page story noting that “the drug prolongs life by only a few months, if that.”<sup>340</sup> One clinician called the results “sobering.”<sup>341</sup> A 2009 editorial on Avastin described its efficacy in breast cancer as “probably nonexistent, even if measured in days.”<sup>342</sup> A 2010 review of several small-effect cancer therapies criticized Avastin as providing only “marginal benefits . . . after it was shown to ‘prolong’ [overall survival] by a statistically insignificant 1.7 months.”<sup>343</sup> And David Gorski, a clinical oncologist and editor of the blog *Science-Based Medicine*, called the approval results “thin gruel.”<sup>344</sup>

Two later follow-on trials of Avastin in breast cancer proved these doubts well-founded. One trial concluded that Avastin *decreased* patient overall survival by 1.1 to 1.7 months; another found that Avastin increased overall survival but only by 2.9 months.<sup>345</sup> This conflicting data—and some additional evidence that Avastin was

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336. FDA, FDA BRIEFING DOCUMENT: ONCOLOGY DRUG ADVISORY COMMITTEE MEETING 7 (2010), <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM219224.pdf> [<https://perma.cc/JQ3P-XVF4>] [hereinafter FDA, AVASTIN].

337. *Id.*

338. *Id.* at 27.

339. *Id.* at 9, 27.

340. Gina Kolata & Andrew Pollack, *In Costly Cancer Drug, Hope and a Dilemma*, N.Y. TIMES, July 6, 2008, at A1.

341. *Id.*

342. Fojo & Grady, *supra* note 21, at 1045.

343. Fojo & Parkinson, *supra* note 21, at 5973.

344. David Gorski, *Avastin and Metastatic Breast Cancer: When Science-Based Medicine Collides with FDA Regulation*, SCI-BASED MED. (Aug. 30, 2010), <https://www.sciencebasedmedicine.org/avastin-and-metastatic-breast-cancer-when-science-based-medicine-collides-with-fda-regulation/> [<https://perma.cc/D3CM-LQ3S>].

345. FDA, AVASTIN, *supra* note 336, at 27.

causing unwanted side effects—eventually caused the FDA to pull approval for Avastin as a treatment of metastatic breast cancer.<sup>346</sup>

Despite all of this, patents on Avastin as a “method of treating breast cancer” abound.<sup>347</sup> For example, U.S. Patent No. 8,017,735, owned by Merck & Co., claims “[a] method for treating [breast] cancer”<sup>348</sup> by using Avastin as a combination therapy with another antibody.<sup>349</sup> U.S. Patent No. 8,859,542, originally assigned to Wyeth Pharmaceuticals, similarly claims “[a] method of treating [breast] cancer”<sup>350</sup> by administering Avastin in conjunction with a triazine derivative.<sup>351</sup> And U.S. Patent No. 9,066,963 claims “[a] method of treating breast cancer in a subject in need thereof”<sup>352</sup> by using Avastin with anthracycline.<sup>353</sup>

Whether such inventions are indeed cancer treatments, as they claim, likely turns on what constitutes a “treatment.”<sup>354</sup> Yet, where the relative effect size of the treatment is so small as to likely be irreproducible—as it was with Avastin—it seems specious to allow patents to claim a drug as a “method of treatment”; it is highly doubtful that the patented drug actually treats the indicated disease. Because a person having ordinary skill in the art would need to engage in undue experimentation to determine whether the claimed therapy constitutes a “method of treating cancer,”<sup>355</sup> cancer treatment patents of this kind are likely invalid for lacking enablement. Such patents are similar to the patent at issue in *In re '318 Patent*,<sup>356</sup> where the cited references concerning a treatment for Alzheimer’s was a “mere research proposal.”<sup>357</sup> Indeed, cancer-treatment patents—like cures for

346. Press Release, FDA, FDA Commissioner Announces Avastin Decision: Drug Not Shown to Be Safe and Effective in Breast Cancer Patients (Nov. 18, 2011), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280536.htm> [<https://perma.cc/NYX8-5UDM>].

347. See, e.g., U.S. Patent No. 9,066,963 col. 289 ll. 20–21 (filed Mar. 15, 2012).

348. U.S. Patent No. 8,017,735 col. 89 l. 51 (filed Nov. 19, 2004).

349. *Id.* col. 95 l. 28.

350. U.S. Patent No. 8,859,542 col. 223 l. 25 (filed Apr. 23, 2014).

351. *Id.* col. 1, l. 25, col. 228 l. 26.

352. '963 Patent col. 289 ll. 20–21.

353. *Id.* col. 290, ll. 20, 31–31.

354. Because the definition of medical treatments could be broad, generally—including interventions that provide little, if any, therapeutic benefit—definitions of cancer treatments may similarly be broadened beyond mere issues of therapeutic efficacy. Cf. Fojo & Grady, *supra* note 21, at 1047 (“Ultimately, however, what counts as a benefit in cancer treatment and how much cost should factor into deliberations are not ethical problems that can be relegated to others.”).

355. See *supra* notes 134–36, 142–52 and accompanying text.

356. *In re '318 Patent Infringement Litig.*, 583 F.3d 1317 (Fed. Cir. 2009).

357. See *id.* at 1324, 1327.

baldness—have been specifically spotlighted by the Federal Circuit as a “notoriously intractable area[]” to prove enablement.<sup>358</sup>

Interestingly, however, this analysis seems to hold despite the ambiguities in enablement doctrine. The skepticism surrounding small effect sizes for therapies in complex diseases is independent of whether enablement is assessed according to the full scope of the contested patent’s claims or only a single embodiment of them.<sup>359</sup> A method of treating cancer dubious at the time of filing is likely to continue being dubious until proven otherwise. Similarly, the difficulties concerning replicating studies with small effect sizes are apparent at the time of filing—as demonstrated by clinicians’ concern with Avastin as a breast cancer therapy before the results of the FDA’s mandated follow-on studies.<sup>360</sup> To that extent, resolving questions of whether postapplication evidence or new scientific advances are allowed to prove a lack of enablement becomes less important.<sup>361</sup> And lastly, the confusing overlap between enablement and lack of utility<sup>362</sup> becomes less confusing where the treatment in question appears, in some senses, useless. As with Avastin, clinicians—and the PTO—are right to ask, “What is the minimum amount of benefit needed to adopt a therapy as the new standard? Is 1.2 months of additional life a ‘good’ in itself?”<sup>363</sup>

### C. *The Social Costs of Irreproducible Drug Patents*

The regulatory history of Prempro, Xigris, Plavix, and Avastin—all drugs once approved and later withdrawn—would suggest a self-correcting mechanism at work: The FDA appears to eventually catch drugs grounded in truly irreproducible data, and demands their discontinuance to the financial detriment of their manufacturers. Drug manufacturers become wary about developing—and, consequently, patenting—irreproducible drugs. And once drugs are removed from the market at the request of the FDA, the patents covering such drugs become worthless because the products that they cover cannot be legally sold.

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358. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917, 924 (Fed. Cir. 2011) (requiring “special procedures . . . for subject matter in once notoriously intractable areas such as cures for baldness or cancer”).

359. For a discussion of these doctrines, see *supra* Part II.B.

360. See *supra* notes 340–44 and accompanying text.

361. See *supra* Part II.A.

362. See *supra* Part II.C.

363. *Fojo & Grady*, *supra* note 21, at 1045.

To the contrary. The proliferation of drug patents grounded in irreproducible data brings with it numerous social costs affecting drug research, scientific integrity, and patient safety. The incentives giving rise to irreproducible patents may have the most startling effect on drug development and research. A recent study by Eric Budish, Benjamin Roin, and Heidi Williams empirically assesses the effects of easy early patenting when combined with the pressures of FDA approval and market races.<sup>364</sup> By examining data concerning cancer clinical trials and firm investment, the authors conclude that “private firms may invest more in late-stage cancer drugs—and *too little* in early-stage cancer and cancer prevention drugs—because late-stage cancer drugs can be brought to market comparatively quickly, whereas drugs to treat early-stage cancer and to prevent cancer require a much longer time to bring to market.”<sup>365</sup>

One of the drivers behind this underinvestment in early-stage treatment and prevention surrounds the “structure of the patent system”<sup>366</sup>: by requiring the patenting of drugs before substantial clinical trials have been conducted—that is, by encouraging irreproducible patents as a condition of economic success—the patent system has encouraged drug developers to focus on treatments that maximize patent life span.<sup>367</sup> This has meant, according to Budish, Roin, and Williams’s data, that private drug developers have practically ignored a core measure of reproducibility in their research: the long-term survival of patients. In fact, there is a *negative* correlation between the percentage of privately sponsored clinical trials and the five-year survival rate of patients enrolled in those trials.<sup>368</sup> And as for development projects that last longer than the patent term—twenty years—“essentially 100 percent are publicly funded.”<sup>369</sup> The incentives of private cancer drug development in the United States, therefore, are to obtain patents quickly on relatively thin data, which can then be used to expedite drug approval on short-term clinical measurements: a recipe for irreproducibility.<sup>370</sup> The cost of this “corporate short-

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364. Budish et al., *supra* note 8, at 2045–46.

365. *Id.* at 2045.

366. *Id.*

367. *See id.* at 2074–75.

368. *Id.* at 2075 fig.5.

369. *Id.* at 2074.

370. *See id.* at 2047–49 (discussing some of the perverse incentives in allowing firms to utilize surrogate endpoints).

termism” is astronomical: “890,000 lost life-years . . . [valued] on the order of \$89 billion.”<sup>371</sup>

Research incentives—and their failures—aside, irreproducible patents also seem to contribute to the opacity of clinical trial data. Besides data obtained from clinical trials themselves, applicants for new drugs must report to the FDA “any other data or information relevant to an evaluation of the safety and effectiveness of the drug product,” including the same preclinical data that are often the subject of a drug’s patents.<sup>372</sup> This discourages applicants from producing—and disclosing in patent applications—robust and potentially invalidating preclinical data. This occurs widely in the diagnostics field, where light regulation has coincided with a recent gold rush to patent basic materials and methods of the art.<sup>373</sup> Approval is easy,<sup>374</sup> the underlying data may be kept confidential,<sup>375</sup> patents are valuable,<sup>376</sup> and robust assessments of reproducibility are scant.<sup>377</sup> This all “creates some unique points of conflict, with consequences for the integrity of the scientific field and for the quality of patient services.”<sup>378</sup>

Similarly, the existence of irreproducible patents further discourages the creation or sharing of clinical information after FDA approval. Patents protecting a new, approved drug are entitled to a presumption of validity, as with all other patents.<sup>379</sup> This presumption means that even baldly irreproducible patents require no further proof of their validity—no follow-on studies as a condition of their issuance. Nonetheless, because postapplication data can be used to invalidate patents in some circumstances,<sup>380</sup> drug developers have little incentive

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371. *Id.* at 2049.

372. 21 C.F.R. § 314.50(d)(5)(iv) (2016).

373. Kane, *supra* note 248, at 838.

374. See Rachel E. Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. DAVIS L. REV. 1881, 1889–93 (2016) (discussing the lack of regulation surrounding many diagnostic tests).

375. ILLUMINA INC., MISEQDX CYSTIC FIBROSIS SYSTEM: PREMARKET NOTIFICATION, 510(K) SUMMARY (2013), [http://www.accessdata.fda.gov/cdrh\\_docs/pdf12/K124006.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf12/K124006.pdf) [<https://perma.cc/LUS7-RVDD>] (marking approval information for the drug MiSeqDx as confidential).

376. See Sherkow & Scott, *supra* note 83, at 260 (discussing the value of diagnostic patents).

377. Lau, Ioannidis & Schmid, *supra* note 9, at 123 (noting that “[t]he number [of meta-analyses] is small compared with the estimate of half a million randomised controlled trials”).

378. Kane, *supra* note 248, at 838.

379. See 35 U.S.C. § 282 (2012) (“A patent shall be presumed valid.”); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917, 923–26 (Fed. Cir. 2011) (concluding that Eli Lilly’s patent satisfied the enablement requirement even though the defendant raised doubts about the studies included in the patent’s specification).

380. See *supra* notes 142–62 and accompanying text.



to engage in follow-on studies in the fear of uncovering harmful data that may cast their patents—or, worse, their FDA approvals—into doubt.<sup>381</sup> Thus, for fear of putting patents into jeopardy, drug manufacturers are encouraged to deprive the medical community of the very sort of information that may elucidate whether the benefits of a particular treatment are, or are not, reproducible.

In addition, irreproducible patents may affect competitors' development programs by discouraging research into and development of alternative uses of known drugs. Because patents on new drugs can be obtained even with sketchy efficacy data,<sup>382</sup> drug developers who receive composition patents on new drugs have a de facto monopoly on all marketable uses of the drug until the original composition patent expires: competitors cannot sell the same drug for a different indication—even if they were the first to run clinical trials for that indication—without receiving a patent license.<sup>383</sup> More pragmatically, all drug developers, focused on short-term goals with limited research budgets, have little incentive to even begin research into alternative uses of known, patented compounds until after those compounds' primary patents expire<sup>384</sup>—even if they suspect that the drug's efficacy data is likely irreproducible.

Finally, irreproducible patents risk becoming weaponized by aggressive patent holders seeking to quash competition in related areas. Patents claiming new effects of old technologies—such as new indications for an old drug—can potentially be used to enjoin competitors from the manufacture or sale of the older pharmaceutical, even if the new indications later turn out to be ineffective.<sup>385</sup> This has recently become an issue in the nutritional supplement industry for

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381. See Eisenberg, *supra* note 24, at 370 (“[T]rial sponsors stand to lose revenue if trials indicate that their products are unsafe or ineffective for certain indications. Indeed, from the perspective of the manufacturer, rigorous clinical trials of off-label uses may be as likely to diminish the value of a particular product as to enhance it.”).

382. See *supra* Parts I.C & III.B.

383. W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 525 (2014) (“Composition patents are more valuable because a patent on the drug’s active ingredient allows the patentee to exclude others from making, selling, or using the drug for any use, even those uses not specifically envisioned by the patentee.”).

384. See Eisenberg, *supra* note 24, at 370; Laakmann, *supra* note 25, at 157–58.

385. See, e.g., *In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 526–28 (Fed. Cir. 2012) (allowing the patentee to assert claims covering virtually all statins, even though the evidence suggested that only a single species was effective); *Cancer Research Tech. Ltd. v. Barr Labs., Inc.*, 625 F.3d 724, 734 (Fed. Cir. 2010) (allowing the patentee to assert claims against a competitor even though it withheld negative clinical study data from the PTO).

patents held by Thermolife International, a nutritional supplement manufacturer. Research in the early 1990s by former Stanford professor John P. Cooke suggested that an amino acid, L-arginine, may increase the natural production of one chemical in the blood, nitric oxide, which had been thought to improve exercise performance.<sup>386</sup> After obtaining patents on this use of L-arginine, however, follow-on research significantly discounted the effect.<sup>387</sup> Nonetheless, Thermolife then purchased the patents from Stanford and began to assert them against competitors selling products merely containing L-arginine—an integral component of virtually all protein powders.<sup>388</sup> Thus, although other supplement manufacturers had been selling L-arginine-containing products for years, and although follow-on research demonstrated that the effect on nitric-oxide production described in the patent was not effective, Thermolife has been able to use these irreproducible patents to wreak havoc through the nutritional supplement industry.<sup>389</sup>

#### IV. THE SIGNIFICANCE OF IRREPRODUCIBILITY TO PATENT LAW

The widespread existence of irreproducible patents—in an area of technology often held as an exemplar of the patent system—shows a broad disconnect between scientific advancement and innovation policy. Unlike peer review, scientific reputation, or grant funding, patents do little to serve as verifiers of truth despite various requirements concerning the disclosure or workability of claimed inventions. Although this disconnect has broad significance for innovation policy, this Article’s findings also have significance for doctrinal patent law.

In particular, this Article illuminates, and potentially resolves, several scholarly debates concerning the role and limits of patents as

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386. See U.S. Patent No. 5,891,459 (filed Nov. 9, 1995); John P. Cooke et al., *Arginine Restores Cholinergic Relaxation of Hypercholesterolemic Rabbit Thoracic Aorta*, 83 CIRCULATION 1057, 1058–61 (1991).

387. Andrew M. Wilson, Randall Harada, Nandini Nair, Naras Balasubramanian & John P. Cooke, *L-Arginine Supplementation in Peripheral Arterial Disease: No Benefit and Possible Harm*, 116 CIRCULATION 188, 188 (2007).

388. Data from LexMachina ([www.lexmachina.com](http://www.lexmachina.com)) show that, as of July 1, 2016, Thermolife has sued at least fifty-four other entities for infringing this and related patents (on file with the *Duke Law Journal*).

389. See *Planet Money: The Muscle Patents*, NPR (June 10, 2016), <http://www.npr.org/templates/transcript/transcript.php?storyId=481597112> [<https://perma.cc/T2HR-KJCJ>] (describing the background of Thermolife’s lawsuits).

collections of scientific information. First, this Article's findings are informative about the limited role of patents as vehicles of scientific disclosure—a hotly debated topic in current scholarship. The presence—and continued validity—of patents grounded in irreproducible data demonstrates that patents are poor conduits of up-to-date, workable, practical disclosures of scientific information. Second, this Article elucidates the difference between the doctrines of utility and enablement: utility concerns whether a patent's claims are *possible*; enablement concerns whether a patent's claims are *probable*. And lastly, this Article suggests a resolution to the continuing problem of whether, and to what extent, enablement should incorporate after-arising evidence: in short, it should. Evidence suggesting that the public *could not* benefit from a patent's disclosures shows that the patentee did not fulfill patent law's quid pro quo—and equally so if the evidence comes before or after the inventor's patent application.

#### A. Irreproducibility and the Limits of Disclosure

Among patent law scholars, there is a robust, recent debate concerning the nature and scope of patent law's disclosure requirement.<sup>390</sup> There appears to be broad consensus that the disclosure requirement, as it is currently structured, does little to inform scientists about critical advances in technology. Jason Rantanen recently compiled academic criticism against this teaching function of patents: “useless,” “incomplete and opaque,” and blind.<sup>391</sup> Jeanne C. Fromer also summarized the “good deal of [empirical] evidence . . . that technologists do not find that [patents] contain[] pertinent information for their research.”<sup>392</sup> Inventors do not read one another's patents, scientists do not cite them in their papers, and patentees do not turn to patents for inspiration.<sup>393</sup> And Timothy R. Holbrook noted that the value of truly cutting-edge information makes patents' supposed “[teaching] function . . . in tension, if not antithetical, to the incentive theory of patent law.”<sup>394</sup>

And yet, many scholars have still lauded the disclosure requirement as an important tool in “bridg[ing] the gap between patent

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390. See *supra* note 129.

391. Jason Rantanen, *Peripheral Disclosure*, 74 U. PITT. L. REV. 1, 6 (2012).

392. Fromer, *supra* note 129, at 560.

393. *Id.* at 560–61.

394. Holbrook, *supra* note 129, at 133.

law and the norms of science.”<sup>395</sup> Sean B. Seymore has proposed several benefits of patents as repositories of scientific information: patents are free, in comparison to expensive academic journals; they are automatically published eighteen months after they are filed; and they serve as outlets for technical information when others are not available.<sup>396</sup> And Dmitry Karshedt has noted that patents may serve as signals of other, more useful information, “such as academic publications and sales of products embodying patented inventions.”<sup>397</sup> Alan Devlin has touted disclosure as simply being better than the alternative: secrecy.<sup>398</sup>

But few have noted the difficulties concerning disclosure with respect to reproducibility.<sup>399</sup> Because patents are static documents, they are poorly equipped to incorporate future findings that cast doubt on their applicability. In the interim, they remain fixed (and enforceable) for twenty years from the date which they were filed—eons in certain fast-moving fields, like computer science. As a consequence, innovators looking for truly informative, technical disclosures in patents may, in many cases, be relying on information that is either out of date or incorrect. And even in cases where patents *do* disclose technical information rapidly, there may be various signs that the data grounding a patent are likely to be irreproducible in the future.<sup>400</sup> The hardest cases, of course, concern patent disclosures that *appear* to be enabling, but later turn out not to be.<sup>401</sup>

These cases—ubiquitous in pharmaceutical patents—strongly counsel against thinking of the disclosure requirement as possessing a teaching function or aligning scientific and legal norms. Patents may

395. *E.g.*, Seymore, *supra* note 29, at 656.

396. *Id.* at 656–57.

397. Dmitry Karshedt, *The Completeness Requirement in Patent Law*, 56 B.C. L. REV. 949, 1016 n.397 (2015).

398. Alan Devlin, *The Misunderstood Function of Disclosure in Patent Law*, 23 HARV. J.L. & TECH. 401, 417–18 (2010). Devlin notes:

[P]atent laws likely were not designed to appeal to the inventors of concealable technology, for whom trade secret is the avenue of greatest allure. . . . [T]he contemporary patent system with its many disclosure conditions would remain unused. Society would be deprived of an understanding of [secret] invention[s] regardless of the patent system’s existence.

*Id.*

399. Dmitry Karshedt is one of the few who has tied together difficulties in the disclosure requirement with reproducibility concerns, albeit in a few narrow cases concerning biotechnology. *See* Karshedt, *supra* note 4, at 110–11.

400. Ioannidis, *Contradicted Effects*, *supra* note 9, at 218, 222.

401. *See supra* Part III.B.1.

very well *appear* to teach others in the field useful information but in fact—and not until long after the patent has issued—not teach anything at all. This view runs counter to some recent scholarship suggesting that the failings of the disclosure function could be solved by making it more robust, by, for example, requiring working examples from patent applicants.<sup>402</sup> Therapies directed to long-term cancer treatments cannot practically be subject to working examples during patent prosecution. And yet, it is precisely such patents that are both financially valuable and subject to charges of irreproducibility. Making the disclosure doctrine more robust in such circumstances would do little to bridge the gap between science and law.

This limited view of disclosure dovetails with recent work concerning the costs and benefits of a dysfunctional disclosure regime. Fromer, for example, has demonstrated just how “disclosure norms and rules are lax.”<sup>403</sup> This, Fromer argues, makes it costly for the public to enforce a more robust disclosure requirement and gives innovation policymakers “good reason to place the costs of adequate informational disclosure on the patent applicant rather than on the public (or the government), to which a greater portion of it is now relegated.”<sup>404</sup> The same is of course true for inventions of suspect reproducibility. The disclosure norms in the pharmaceutical context are substantially lax as compared to the regulatory work required to bring products to market. But heightening reproducibility requirements at the PTO by requiring more robust preclinical data may not be worth the candle in light of subsequent regulatory delay.

As a consequence, patents that disclose irreproducible data suggest only the narrowest of teaching functions, if they have one at all. Even under the best circumstances—drugs, like Prempro, that have gone through robust clinical trials, only to have *more* robust clinical trials undermine their efficacy—it is unclear what was gained from the disclosures in the patent document.

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402. *E.g.*, Eisenberg, *supra* note 130, at 214–16; Fiona E. Murray, Joshua S. Gans & Mackey L. Craven, *How Does the Republic of Science Shape the Patent System? Broadening the Institutional Analysis of Innovation Beyond Patents*, 1 U.C. IRV. L. REV. 357, 360 (2011); Seymore, *supra* note 29, at 654–56.

403. Fromer, *supra* note 129, at 596.

404. *Id.*

### B. Irreproducibility and Utility

Like the Federal Circuit in *Eli Lilly*, scholars have traditionally linked utility and enablement.<sup>405</sup> Dan L. Burk and Lemley, for example, famously described the connection in 2004: “[T]he definition of enablement affects the patentability requirement of specific utility, as the invention must operate as described in the specification if the inventor is to enable one of ordinary skill to use it.”<sup>406</sup> At the same time, little scholarly attention has been focused on qualifying which doctrine should apply depending upon *how many* embodiments of an invention may make its patent’s claims inoperative. This has resulted in at least some of the confusion in how to appropriately assess patents claiming broad genres of their technologies,<sup>407</sup> after-arising embodiments,<sup>408</sup> or cases where “some members of [embodiments] *x* have utility, and some do not.”<sup>409</sup>

This Article’s recognition that irreproducibility may render some patent claims useful but not enabling suggests one avenue of relief: the overlap between utility and enablement only appears meaningful where *no* embodiments of the claims are workable.<sup>410</sup> By contrast, because of the varied nature of irreproducibility,<sup>411</sup> patents grounded in irreproducible data do not necessarily fail in all cases—and as a consequence, the two doctrines appear to work independently. Indeed, utility only appears to serve as a proxy for enablement when follow-on studies produce contradictory results.<sup>412</sup> When future studies are simply unable to replicate prior results,<sup>413</sup> or produce effect sizes

405. See, e.g., Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERKELEY TECH. L.J. 1141, 1164 n.78 (2008); Seymore, *supra* note 210, at 1068 (“Under current law, an invention which lacks utility under § 101 also fails as a matter of law to comply with the enablement requirement of § 112(a).”).

406. Dan L. Burk & Mark A. Lemley, *Biotechnology’s Uncertainty Principle*, 54 CASE W. RES. L. REV. 691, 709 (2004).

407. See Michael Risch, *A Surprisingly Useful Requirement*, 19 GEO. MASON L. REV. 57, 102 (2011) (“The difficult question is determining whether the specification has enabled the broad genus.”).

408. See Collins, *supra* note 13, at 1098–1105.

409. Lefstin, *supra* note 405, at 1164 n.78.

410. See *supra* notes 227–34 and accompanying text.

411. For a demonstration of the heterogeneity of irreproducibility in pharmaceuticals, see *supra* Part III.B.

412. For a discussion of Prempro, see *supra* Part III.B.1.

413. See Drummond, *supra* note 4, at 2. For a discussion of Xigris, see *supra* Part III.B.2.

smaller or larger than those determined originally,<sup>414</sup> this does not mean that inventions based on earlier studies fail as a matter of course. Put more pithily, one way to recognize the difference between utility and enablement is this: utility concerns *possibility*; enablement concerns *probability*.

This understanding should also be useful for courts addressing similar questions concerning reproducibility. A patent with claims drawn to several irreproducible—and disabling—embodiments but with a single enabling embodiment still possesses utility; the patent has *a* use for persons having ordinary skill in the patent's art. Invalidating such a patent on utility grounds would consequently be wrong as a matter of doctrine.<sup>415</sup> Nor would it fulfill the purpose of the utility requirement to prohibit the patenting of trivial or useless inventions.<sup>416</sup> The doctrine of enablement, rather—the doctrine concerning the strength and accuracy of the patent's disclosure—seems much better suited to the task of invalidating patents claiming multiple irreproducible embodiments. Courts looking to utility to resolve questions of irreproducibility rather than enablement therefore have the potential to hamstring themselves by only invalidating impossible or contradictory patents. Clearly differentiating the two doctrines would provide courts a single, clear avenue to assess claims of disabling irreproducibility.

### C. Irreproducibility and After-Arising Evidence

Lastly, the nature of irreproducible patents also strongly favors current scholarly—and judicial—trends calling for the introduction of postapplication evidence to prove a lack of enablement.<sup>417</sup> As highlighted by *In re '318 Patent* and *Eli Lilly*, enablement sets no clear rules for when postapplication evidence can be introduced to challenge—or support—a patent's validity.<sup>418</sup> This is problematic for

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414. See Ioannidis, *Contradicted Effects*, *supra* note 9, at 222 (describing different effect sizes in follow-on clinical studies). For a discussion of using Avastin to treat breast cancer, see *supra* Part III.B.4.

415. See Seymore, *supra* note 210, at 1048 (“A low utility threshold aligns with the broad policy goals of the patent system.”).

416. See *id.* at 1075–76.

417. See *supra* Part II.A.

418. *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 925–26 (Fed. Cir. 2011) (allowing future evidence to satisfy enablement); *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1327 (Fed. Cir. 2009) (disallowing postapplication evidence to satisfy enablement); see also *supra* Part II.A.

patents based on irreproducible data because the nature of irreproducibility is post hoc: whether a study is or is not reproducible can only be determined after the original study has been completed.<sup>419</sup>

This has several normative advantages. Allowing postapplication evidence in enablement assessments would therefore strongly discourage patents fixed in irreproducible data. Patentees faced with the choice of filing early applications based on skimpy—and likely irreproducible—data, or waiting to perfect their applications with more robust data, should, all else equal, choose the latter. Patent applicants without such options may consider narrowing their claims to better encompass the certainty—or lack thereof—of their inventions. And challengers of putatively invalid patents would be encouraged to spend litigation resources demonstrating the irreproducibility of the patents asserted against them—a rare example of litigation strategy and scientific advancement aligning. In any of these cases, opening patent challenges to postapplication evidence weeds irreproducible data from the greater patent landscape.

As indicated by the diverging opinions in *In re '318 Patent* and *Eli Lilly*, the role of postapplication evidence in enablement challenges is governed judicially.<sup>420</sup> And there is nothing in the enablement statute to suggest that postapplication evidence should never be considered in raising questions of enablement.<sup>421</sup> The Federal Circuit should therefore explicitly permit the introduction of postapplication evidence to challenge irreproducible patents' lack of enablement—with several boundaries.

First, a long line of enablement precedent has defined the doctrine as whether a person having ordinary skill in the art could have made and used the invention without undue experimentation *at the time of the patent application*.<sup>422</sup> Accordingly, the ultimate inquiry for whether postapplication evidence proves the invalidity of an issued patent should be worded as whether the postapplication evidence demonstrates that a person having ordinary skill in the art could not have made or used the invention *at the time of the patent application*.

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419. See Stodden, *supra* note 4, at 1 (“A fundamental goal of statistics is to ensure the reproducibility of scientific findings. . . . If discoveries are made, it is of great interest to understand whether these findings persist in different samples . . . . The persistence of findings across different samples is the basis upon which scientific claims are evaluated.”).

420. See *Eli Lilly*, 435 F. App'x at 925–26; *In re '318 Patent*, 583 F.3d at 1327.

421. See 35 U.S.C. § 112 (2012).

422. See Collins, *supra* note 13, at 1098–1105 (discussing these cases); see also Lemley, *supra* note 13, at 106–07 (discussing this in the context of claim interpretation).



This standard seems squarely in line with the enablement statute. Currently codified at 35 U.S.C. § 112(a), it makes no mention of when enablement evidence must have been published or created, or even when the enablement inquiry arises. It requires only that the specification enable others to “make and use” the invention.<sup>423</sup> Further, allowing postapplication evidence to assess enablement traces the basic contours of a scientific understanding of irreproducibility, an inquiry typically focused on whether an original study was, in fact, true to begin with.<sup>424</sup>

Second, the introduction of postapplication evidence to combat enablement should not turn on whether the issue was raised by the patent examiner during prosecution, in contravention of *Eli Lilly*.<sup>425</sup> Patent prosecution is, in many senses, “an ongoing negotiation between the PTO and the applicant.”<sup>426</sup> Formal challenges by the examiner to the apparent irreproducibility of a patent application’s claims therefore likely turn on the content of negotiations—or lack thereof—between an applicant and the PTO. Such challenges may also reflect the drafting skill of the patent attorney or the whim of the examiner, rather than the level of irreproducibility of the patent application’s source data. Future challengers to issued patents should not be precluded from raising similar issues simply because the examiner was slack.<sup>427</sup>

Third, postapplication evidence should not be limited to only “notoriously intractable areas such as cures for baldness or cancer.”<sup>428</sup> Other areas of scientific inquiry—and patenting—similarly suffer from irreproducible data, such as genetic testing,<sup>429</sup> antibody research,<sup>430</sup> and

423. 35 U.S.C. § 112(a). The statute states:

The specification shall 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, or with which it is most nearly connected, to make and use the same . . . .

*Id.*

424. See Ioannidis, *Research Findings*, *supra* note 9, at 696 (describing reproducibility as the circumstance in which “research findings are compared against the gold standard of true relationships in a scientific field”).

425. See *Eli Lilly*, 435 F. App’x at 924–25.

426. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005).

427. *Cf. The T.J. Hooper v. N. Barge Corp.*, 60 F.2d 737, 740 (2d Cir. 1932) (“[W]hen some have thought a device necessary, at least we may say that they were right, and the others too slack. . . . [But this] does not bear on [liability] at all.”).

428. *Eli Lilly*, 435 F. App’x at 924.

429. Ioannidis et al., *Replication Validity*, *supra* note 9, at 306; Kane, *supra* note 248, at 838.

430. Baker, *supra* note 86, at 274.

even social sciences.<sup>431</sup> Because enablement is assessed for each patent— independent of its field of art— patents in less “intractable” fields may still suffer from irreproducible results. Those patents should be no less subject to postapplication evidence.

Demanding a full-scope analysis would therefore have the beneficial effect of invalidating broad patents that cover irreproducible embodiments—a sensible interpretation of the patent statute’s requirement that patents must inform their users to “make and use” the invention.<sup>432</sup> It would also strongly discourage patentees from filing overbroad claims in the first instance, and patentees would either rely on stronger data to prove their possession of the invention or narrow their claims to comport with the data they have. Irreproducible patents—such as those broadly claiming “a method of treating cancer” where preclinical trials suggest only a narrower indication—would consequently run afoul of this proscription.<sup>433</sup>

To be sure, embracing the full-scope doctrine has disadvantages. It cuts against the principle that patent claims can—and sometimes should—encompass after-arising technologies.<sup>434</sup> Inventors, for example, may be able to fully possess and describe their *claims*—even if they are unaware of precise applications of their technologies.<sup>435</sup> And a full-scope doctrine suffers from the fact that, at some level, “[t]here is always an unforeseen embodiment that falls within a claim.”<sup>436</sup> Bernard Chao has linked this principle to essential fairness: “[A] claim should not be invalidated simply because the inventor did not foresee every embodiment that may eventually fall within its scope.”<sup>437</sup>

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431. Stodden, *supra* note 4, at 3–4.

432. *See supra* note 423.

433. *See* Holbrook, *supra* note 129, at 157–58. Holbrook notes:

Enablement doctrine performs this role of confining the scope of the claims to what the inventor actually possessed. . . . This limit on the scope is particularly important in unpredictable art fields. For example, if a patentee discovers a cure for ovarian cancer, she likely will not be able to claim curing *all* forms of cancer. She can only claim that which the PHOSITA objectively recognized would be in the inventor’s possession.

*Id.*

434. *See* Chao, *supra* note 14, at 1378 (“[A] claim should not be invalidated simply because the inventor did not foresee every embodiment that may eventually fall within its scope.”); Collins, *supra* note 13, at 1084–85 (arguing that some instances of after-arising technology should be covered by earlier-drafted claims); Holbrook, *supra* note 129, at 158 (“To require disclosure of every variant would be extremely costly and burdensome to both the applicant and the PTO.”).

435. *See, e.g.,* Collins, *supra* note 13, at 1107–08 (discussing this in the context of protein identification and synthesis); Feldman, *supra* note 13, at 20–21 (discussing interferons); Lemley, *supra* note 13, at 116–17 (discussing antibodies).

436. Chao, *supra* note 14, at 1378.

437. *Id.*

But it is one thing to allow claims to encompass unforeseen developments in technology and another to allow them to cover technologies that failed to work when they were drafted. Supporting the former simply further encourages the drafting of overbroad claims, one of the central problems in patents today.<sup>438</sup> Further, these criticisms of the full-scope doctrine seem to be outweighed by the heft of enablement's purpose: that inventors should only be allowed to patent that which they can teach others to make and do.<sup>439</sup> Aligning the full-scope doctrine with enablement would do much to ensure that patent claims are actually enabled rather than being irreproducible. The solution is to simply require patentees to draft their claims more narrowly where the possibility of future disabling evidence is low.

### CONCLUSION

Although scientific and technological progress ultimately depend on reproducibility, patent law—and the doctrine of enablement, in particular—does little to promote it. Enablement's ambiguities concerning the role of postapplication evidence, the scope of the enablement inquiry, and the doctrine's relationship with utility all remain unresolved and favor patents grounded in early, irreproducible data. Pharmaceutical patents seem especially susceptible to these incentives encouraging irreproducibility—with truly problematic results. The widespread existence of such patents informs us a great deal about the true role of enablement in patent law. It strongly suggests that reproducibility analyses should factor into enablement determinations: patents that disclose irreproducible inventions simply fail to enable others to “make and use” the claimed inventions. It also demonstrates the limits of patents as vehicles of scientific disclosure. And it resolves the current doctrinal tension between utility and enablement. These lessons concerning reproducibility in patent law should better align scientific practice with innovation policy and prevent the current incentive structure of disablement.

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438. See Mark A. Lemley, Michael Risch, Ted Sichelman & R. Polk Wagner, *Life After Bilski*, 63 STAN. L. REV. 1315, 1339–41 (2011) (describing the problem of overbreadth in identifying the “abstract idea” of a patent's claims). See generally Mark A. Lemley & Mark P. McKenna, *Scope*, 57 WM. & MARY L. REV. 2197 (2016) (discussing the idea of scope across intellectual property disciplines).

439. See Seymore, *supra* note 29, at 652 (“[T]he teaching function and enablement are inextricably related . . .”).