DISENABLEMENT: SCIENTIFIC IRREPRODUCIBILITY IN PATENT LAW

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ABSTRACT

Reproducibility—the verification of scientific results by outside researchers—lies at the heart of the scientific method. And yet, it forms little part of the law most connected with science and technology: patent law. To the contrary, the most salient patent law doctrine in this area—enablement—appears to mitigate or even actively dissuade litigation concerning reproducibility. This is critically problematic in the context of pharmaceutical patents, where some of the most valuable patents appear based on ultimately irreproducible data. This Article attempts to reconcile the enablement doctrine with irreproducibility by assessing some of the difficulties in enablement doctrine, generally, and exploring recent concerns with scientific irreproducibility. It also provides several concrete examples of irreproducibility in patents on blockbuster drugs—Prempro, Xigris, Plavix, and Avastin. Lastly, the Article provides several suggestions for encouraging reproducible data in patents, including clarifying the enablement doctrine, easing patent law's statutory bars for empirically-based inventions, and mandating open access to testing data. These modifications would align patent law, scientific practice, and innovation policy, and prevent the current incentive structure of disenablement.

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INTRODUCTION

Reproducibility—the verification of scientific results by outside researchers—lies at the heart of the scientific method.[1] And yet, it forms little part of the law most connected with science and technology: patent law. To the contrary, the most salient patent law doctrine in this area—enablement—appears to mitigate or even actively dissuade litigation concerning reproducibility.[2] This is critically problematic in the context of pharmaceutical patents, many of

[1] *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 2002) ("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—stands up to the demands of the practice, whether raised purely by scientific experiments, or by practical technological applications."); Dmitry Karshtedt, *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, 2443 (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. STATISTICS APPLICATIONS 1, 2-4 (2015) ("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.").

To be clear, reproducibility and replicability are related but distinct concepts, and the differences between them may be nuanced. 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), *available at* http://cogprints.org/7691/7/icmlws09.pdf. To the extent these concepts can be separated, this Article focuses on what can be considered classical reproducibility—whether the results of a scientific experiment are, in some greater sense, "true." *See* POPPER, *supra* note 1, at 195 ("*[T]he idea of a reproducible physical effect*—an idea which is closely connected with that of objectivity.").

[2] *See, e.g.*, In re '318 Patent Infringement Litig., 583 F.3d 1317, 1327 (Fed. Cir. 2009) (disallowing post-application evidence to satisfy enablement); Schering Corp. v. Amgen Inc., 222 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 (Fed. Cir. 1988) (rejecting evidence that patent failed to disclose an important method of practicing the invention).

which are worth billions of dollars but are nonetheless based on irreproducible data.[3] Taken seriously, these reproducibility concerns counsel invalidating some of the most valuable intellectual property rights in existence—a potentially catastrophic drain on innovation. Ignored, and patent law appears to grant exclusive rights to inventions based on spurious scientific results, at significant social costs.[4] This doctrine of "disenablement" highlights one of the starkest differences between the operation of science and patent law. This Article seeks to explain these differences and reconcile them.

Some of this disconnect stems from the enablement doctrine itself. Because patents serve as a quid pro quo—inventors publicly disclose their inventions in return for exclusionary rights—patent law governs the substance and form of inventors' disclosures.[5] To that end, the doctrine of enablement canonically requires patents "to enable any person skilled in the art to which it pertains . . . to make and use" the invention.[6] But this distillation of enablement complicates as many issues as it simplifies. For example, 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.[7] Courts have also had difficulty measuring the breadth of the doctrine: whether it applies to the full scope of a patent's claims or

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[3] *See* Francis S. Collins & Lawrence A. Tabak, *NIH Plans to Enhance Reproducibility*, 505 NATURE 612 (2014) (discussing reproducibility in the context of preclinical drug studies); Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012*, 311 JAMA 368 (2014) (empirically assessing the reproducibility of new, presumably patented, drugs); Douglas F. Easton et al., *Gene-Panel Sequencing and the Prediction of Breast Cancer Risk*, 372 NEW ENGL. 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 JAMA 218 (2005) [hereinafter Ioannidis, *Contradicted Effects*] (examining the irreproducibility of several high-profile drugs); John P.A. Ioannidis et al., *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 is 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).

[4] *See, e.g.*, Eric Budish, Benjamin Roin, & Heidi Williams, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044, 2077 (2015) (describing some of the effects of easy, irreproducible patenting on pharmaceutical developers' research pipelines).

[5] *See* 35 U.S.C. § 112 (2013); 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.").

[6] 35 U.S.C. § 112(a) (2013).

[7] *See* Kevin Emerson Collins, *Enabling After-Arising Technology*, 34 J. CORP. L. 1083, 1098-1105 (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 where claim terms appear to have changed due to later scientific advances).

merely a subset.[8] The doctrine also seems to be confusingly intertwined with another patent law doctrine—utility—that only appears to overlap in narrow cases.[9] And courts have never resolved whether later scientific advances can be used to retroactively demonstrate that a patent's description of an invention, at the time it was filed, did not, in fact, produce the results it contemplated.[10] Despite enablement's lengthy existence,[11] these issues have yet to be resolved.

The remainder of the disconnect between science and patent law results from science's dynamism—its continuous resolution of prior inconsistencies. 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.[12] Advances in scientific technique and computerized methodology have recently brought the importance of reproducibility into the spotlight. Several major papers have raised the specter that many large and expensive research efforts are, in fact, irreproducible.[13] These warnings are particularly poignant in the context of new therapeutics, where studies mandated—and approved—by the Food and Drug Administration (FDA) have later been cast into doubt.[14] In 2014, Francis S. Collins, the former Director of the National Institute of Health (NIH), remarked on the "troubling frequency of published reports that claim a significant result, but fail to be reproducible."[15]

As a consequence, enablement's lack of concern for reproducibility has had a pernicious effect on innovation. In the therapeutics context, a gulf has widened between the bounty of FDA approval and the minimal requirements to obtain a patent. Pharmaceutical developers now have powerful incentives to apply for patents early, on little and irreproducible data, independent of the ultimate value—or even approval—of the drug.[16] Indeed, the patents for several blockbuster

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[8] *See* Bernard Chao, *The Infringement Continuum*, 35 CARDOZO L. REV. 1359, 1378 (2014) (describing this difficulty as "unworkable").

[9] *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").

[10] *See* Lemley, *supra* note 7, at 106-07.

[11] *See* Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERKELEY TECH. L.J. 1141, 1202 (2008) (discussing the pedigree of enablement).

[12] *See, e.g.*, THOMAS S. KUHN, THE STRUCTURE OF SCIENTIFIC REVOLUTIONS 111 (3d ed. 1996) ("[A]fter a revolution scientists are responding to a different world.").

[13] Collins & Tabak, *supra* note 3, at 612; Downing et al., *supra* note 3, at 368; Easton et al., *supra* note 3, at 2243; Ioannidis, *Research Findings*, *supra* note 3, at 696; Ioannidis, *Contradicted Effects*, *supra* note 3, at 218; Ioannidis et al., *Replication Validity*, *supra* note 3, at 306; Lau, Ioannidis, & Schmid, *supra* note 3, at 123; Leek & Peng, *supra* note 3, at 612; Randall J. LeVeque, Ian M. Mitchell, & Victoria Stodden, *Reproducible Research for Scientific Computing: Tools and Strategies for Changing the Culture*, COMPUT. SCI. ENG'R 13 (July/Aug. 2012); Light & Lexchin, *supra* note 3, at H2068; Stodden, *supra* note 1, at 1; The Yale Law School Roundtable on Data and Code Sharing, *supra* note 153, at 8.

[14] *See, e.g.*, Ioannidis, *Contradicted Effects*, *supra* note 3, at 218 (describing 45 such studies).

[15] Collins & Tabak, *supra* note 3, at 612.

[16] *See* Christopher A. Cotropia, *The Folly of Early Filing in Patent Law*, 61 HASTINGS L.J. 65, 93-96 (2009) (describing the negatives of early patent filing); 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); 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*

drugs, such as Prempro, Xigris, Plavix, and Avastin, have held fast even while the FDA has withdrawn its approval of such drugs due to their lack of reproducible efficacy data.[17] This incentive to patent outweighing the incentive to meaningfully innovate bears significant social costs: it motivates pharmaceutical manufacturers to develop easily patentable but clinically meaningless drugs;[18] it encourages data secrecy;[19] and it dissuades competitors from researching alternative uses to known, patented therapeutics.[20] For cancer drugs in particular, this disconnect between easy patenting and difficult clinical trials has encouraged drug developers to research weak but easily patentable and approvable treatments over more difficult cures and preventative therapeutics.[21] 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."[22]

As with other failures in innovation policy, there are likely many ways to solve these difficulties.[23] But perhaps the most politically administrable and judicially expedient method lies in reforming patent law—and the doctrine of enablement, in particular—to acknowledge and respond to claims of irreproducibility. First, at a broader scale, enablement needs to be clarified to resolve the outstanding issues concerning scope, post-application evidence, and the doctrine's relationship with utility. Doing so will provide patent applicants—as well as litigants—certainty as to how to manage claims of irreproducibility. Ideally, it would discourage the shotgun filing of patent applications on weak, irreproducible data. Second, Congress should relax patent law's current strictures on using inventions prior to patenting them—patent law's statutory bars.[24] Relaxing these provisions, especially for complex inventions like therapeutics, would encourage inventors to further refine and better disclose their inventions, countering several basic irreproducibility problems. And third, in the pharmaceutical context, the FDA should make preclinical and clinical trial data publicly accessible. Where such data contains the indicia of irreproducibility, this would check applicants' use of the same data in patent applications.

Little by Giving Too Much?, 16 CLINICAL CANCER RES. 5972, 5973 (2010) (criticizing the FDA approval process for narrow therapies of patented medications).

[17] *See infra* Part III.B.

[18] Budish, Roin, & Williams, *supra* note 4, at 2077 (discussing tamoxifen); Fojo & Grady, *supra* note 16, at 1045 (cetuximab).

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

[20] *See id.* at 370; ANNA B. LAAKMANN, INTELLECTUAL AND REGULATORY PROPERTY 50 (March 2015) (unpublished manuscript on file with the author) ("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.").

[21] Budish, Roin, & Williams, *supra* note 4, at 2049.

[22] *Id.*

[23] *See, e.g.*, Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents–Prizes Debate*, 92 TEX. L. REV. 303 (2013) (describing solving several innovation policy problems using research-and-development tax incentives); Lisa Larrimore Ouellette, *Patent Experimentalism*, 101 VA. L. REV. 65 (2015) ("Do patents provide a net innovation incentive? Are other incentives—such as prizes, grants, or research tax incentives—superior?").

[24] *See* Cotropia, *supra* note 16, at 81 (describing some of the negative policy implications of the statutory bars).

Aligning patent law with science here would create better outcomes—for patent doctrine, scientific research, and the consuming public.

Part I of this Article reviews the doctrine of enablement, and its difficulties, with respect to reproducibility. Part II examines the norm and importance of reproducibility in science, as well as recent concerns over irreproducibility, especially in context of clinical trials. 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—Prempro, Xigris, Plavix, and Avastin. And it also details some of the social costs of such a system. Lastly, Part IV provides some solutions for encouraging reproducibility in patent law.

I. THE TIMING AND SCOPE OF ENABLEMENT

Patents have long been described as a quid pro quo: the government grants to inventors the exclusive rights to their inventions so long as they sufficiently disclose them.[25] With an inventor's disclosure, the public receives the technical knowledge contained in the patent as soon as it is published. After the patent has expired, the public may then use and improve the invention without paying a royalty.[26] This incentive to transfer knowledge is the mechanism—at least, ideally—by which patents "promote the Progress of Science and useful Arts."[27]

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[25] 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. 1, 23 (1829) ("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.").

[26] Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1022 (1989) ("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."); Sean B. Seymore, *The Teaching Function of Patents*, 85 NOTRE DAME L. REV. 621, 624 (2010) ("[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.").

[27] U.S. CONST., art. I, § 8, cl. 8. Whether this ideal holds up in practice remains controversial. *See, e.g.*, Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1623 (2003) (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*

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.[28] At the same time, the lay public cannot be expected to understand even valuable patent disclosures in highly technical fields.[29] Garage-shop tinkerers are not expected to understand patents in the rocket sciences; rocket scientists' patents should not be invalid for not educating them.

The patent statute 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."[30] 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.[31] 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.[32] This analysis makes "enablement, while conceptually simple . . . legally and factually complex."[33] In all, enablement acts as one of the "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."[34]

Patent Doctrine, 79 U. COLO. L. REV. 467, 485–88 (2008) (proposing that user-innovators' disclosure preferences are not matched by the patent system).

[28] *See* Fromer, *supra* note 26, at 552-53 ("[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.").

[29] *See* Mark D. Janis & Timothy R. Holbrook, *Patent Law's Audience*, 97 MINN. L. REV. 72, 114 (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."); 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); Seymore, *supra* note 26, at 641 (describing the patent document as a potential, and routinely unfulfilled, source of technical information).

[30] 35 U.S.C. § 112(a) (2011) (emphasis added).

[31] In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

[32] *Id.* Notably, these factors are "illustrative, not mandatory." Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1213 (Fed. Cir. 1991).

[33] Holbrook, *supra* note 26, at 129.

[34] Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 982 (Fed. Cir. 2002) (Rader, C.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.

Ironically, however, it appears that the enablement doctrine is not fully enabling—that is, several basic questions regarding its application remain unresolved and difficult to practice. First, the timing of the enablement determination—*when* enablement should be assessed—is indeterminate. Recent cases from the Federal Circuit have presented conflicting views on whether evidence obtained after a patent application has been filed can used to prove enablement.[35] Second, the Federal Circuit has cobbled together a fractured jurisprudence on the scope of the enablement determination—whether, for example, the full scope of a patent's claims must be enabled or only a single embodiment.[36] Third, in some instances, courts have confusingly amalgamated some aspects of enablement with a different patent doctrine—utility—to create a peculiar hybrid doctrine, "enablement utility."[37] And fourth, the doctrine has so far failed to sufficiently address how it interacts with advances in science that take place after a patent has issued—whether, for example, future research could alter the meaning of a claim term from an enabling definition to a disenabling one.[38] These problems each show the difficulties in applying the enablement doctrine to evolving information.

A. Post-Application Evidence

Ostensibly, the "enablement determination is made *retrospectively, i.e.*, 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."[39] 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.[40] In *In re '318 Patent Infringement Litigation*, for example, the Federal Circuit affirmed the invalidation of the plaintiffs' patent covering a method

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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").

[35] *Compare* In re '318 Patent Infringement Litigation, 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).

[36] *Compare* Mag-Sil Corp. v. Hitachi Global Storage Techs., Inc., 687 F.3d 1377, 1384 (Fed. Cir. 2013) (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 the enablement requirement is satisfied "if the description enables *any* mode of making and using the claimed invention") (emphasis added).

[37] *See Eli Lilly*, 435 F. App'x at 925-26.

[38] *See* Collins, *supra* note 7, at 1098-1105 (discussing this difficulty concerning unforeseeable "after-arising" technology); Feldman, *supra* note 7, 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 7, at 106-07 (discussing several cases where claim terms appear to have changed due to later scientific advances).

[39] Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371-72 (Fed. Cir. 1999).

[40] *See* Collins, *supra* note 7, at 1087 ("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]."); Sean Seymore, *Heightened Enablement in the Unpredictable Arts*, 56 UCLA L. REV. 127, 142 (2006) ("[T]he Examiner cannot use a reference to show lack of enablement based on later developments in the art.").

of treating Alzheimer's disease using galantamine, a common alkaloid extracted from various flowers.[41] 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."[42] This, the Federal Circuit concluded, was a "mere research proposal"[43] 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."[44] The fact that later studies proved the inventor's hypothesis true,[45] or that the FDA eventually approved galantamine to treat Alzheimer's,[46] was irrelevant.

But later research that illuminates a patent's claims is not always irrelevant. In *Eli Lilly & Co. v. Actavis Elizabeth LLC*, the Federal Circuit reversed the district court's conclusion that Eli Lilly's patent was invalid for lacking enablement.[47] The patent covered a method for treating attention-deficit hyperactivity disorder (ADHD) using a newly created drug, atomoxetine.[48] After a bench trial, the district court concluded that the patent was invalid for lacking enablement: "the prior art stressed that the mechanism of action of ADHD was unclear at the time the patent application,"[49] the "patent contained no test data,"[50] and at time of the patent's application, no clinical trials had been performed.[51] Even the inventor testified at his deposition, "I wasn't sure at all that it would work."[52] 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."[53] 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

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[41] 583 F.3d 1317 (Fed. Cir. 2009); *see also* Michael Heinrich, *Snowdrops: The Heralds of Spring and a Modern Drug for Alzheimer's Disease*, 273 PHARMA. J. 905 (2004).

[42] In re '318 Patent Infringement Litig., 583 F.3d 1317, 1321 (Fed. Cir. 2009).

[43] *Id.* at 1324.

[44] *Id.* at 1323 (quoting In re '318 Patent Infringement Litig., 578 F. Supp. 2d 711, 732 (D. Del. 2008)) (alterations in original).

[45] *See id.* at 1328 (Gajarsa, J., dissenting) ("[L]ater animal studies and human clinical trials proved and confirmed galantamine's effectiveness.").

[46] Letter from Robert Temple, M.D., Director, Office of Drug Evaluation I, to Charles LaPree, Assistant Director, Regulatory Affairs, Janssen Research Foundation (Feb. 28, 2001), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2001/21169ltr.pdf.

[47] 435 F. App'x 917 (Fed. Cir. 2011).

[48] Eli Lilly & Co. v. Actavis Elizabeth LLC, 731 F. Supp. 2d 348, 351-52 (D.N.J. 2010).

[49] *Id.* at 386.

[50] *Id.* at 389.

[51] *Id.* at 387-88.

[52] *Eli Lilly*, 435 F. App'x at 923.

[53] *Id.* at 924.

can be falsified,"[54] 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 areas such as cures for baldness or cancer."[55]

Reconciling these two cases—and developing a working standard for when enablement can be demonstrated with post-application evidence—remains difficult. In *Eli Lilly*, the court attempted to reconcile its decision with *In re '318 Patent* by claiming that the patent in *In re '318 Patent* did not contain "a reasonable correlation between [the] compound's activity and its asserted therapeutic use."[56] Eli Lilly's application, on the other hand, did reasonably describe a therapeutic relationship, albeit on a related but different drug.[57] But this distinction seems to negate the enablement standard: 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—clinical trials—to determine whether the claimed drug worked as indicated. Indeed, in both *In re '318 Patent* and *Eli Lilly*, the patent owners still needed to shepherd their patented drugs through years of clinical trials, simply to determine whether they worked at all.[58]

Other avenues for reconciling the divergent standards in *In re '318 Patent* and *Eli Lilly* also seem suspect. Because the PTO examiner raised a lack of enablement during the application process in *In re '318 Patent*,[59] but not in *Eli Lilly*,[60] the cases may simply stand for the proposition that if the issue is raised during patent prosecution, inventors are barred from using post-application evidence to save their patents. But such a distinction seems especially problematic because accused infringers are entitled to defend their lawsuits by proving that the patent lacks almost any condition for patentability specified by the patent statute, irrespective of whether the lack of those conditions were raised by the original patent examiner.[61] Or, it may be that the Federal Circuit considers treatments for Alzheimer's disease, but not ADHD, to be in the same class as "cures for baldness or cancer," cases that "warrant the special procedures that are authorized for use when the examiner doubts the described utility."[62] The science (or law) for such a distinction, though, seems lacking.[63] Or it may be that patents on new drugs are more

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[54] *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)).

[55] *Id.*

[56] *Id.* at 926.

[57] *Id.* at 926.

[58] *See* In re '318 Patent Infringement Litigation, 583 F.3d 1317, 1328 (Fed. Cir. 2009) ("[L]ater animal studies and human clinical trials proved and confirmed galantamine's effectiveness.") (Gajarsa, J., dissenting); *Eli Lilly*, 435 F. App'x at 919-20 (recounting the clinical trial history of atomoxetine).

[59] *See* In re '318 Patent Infringement Litig., 583 F.3d 1317, 1322 (Fed. Cir. 2009).

[60] *Eli Lilly*, 435 F. App'x at 924 ("During examination of the '590 application, the patent examiner did not require the submission of data showing treatment of ADHD with atomoxetine . . . .").

[61] *See* 35 U.S.C. § 282(b) (2011).

[62] *See id.*

[63] *See* Patrick F. Sullivan, Mark J. Daly & Michael O'Donovan, *Genetic Architectures of Psychiatric Disorders: The Emerging Picture and Its Implications*, 13 NATURE REV. GENETICS 537, 551 (2012) (describing both Alzheimer's disease and ADHD, among other psychiatric illnesses, as "intractable enigmas in medicine").

likely to be enabling than patents on older drugs used for new indications—a proposition that is entirely counterintuitive and runs against the clinical trial history presented in favor of upholding the patent in *Eli Lilly*.[64]

None of these distinctions seem particularly satisfying, and the cases seem better as markers of the Federal Circuit's recent difficulties in assessing post-application evidence than as guideposts of the enablement doctrine. Litigants continue to rely on post-application evidence to make their arguments concerning enablement. Whether the court will admit such evidence, or whether it is ultimately persuasive, remains elusive.

B. The Scope of Inquiry

Section 112(a) of the patent statute requires a patent's "specification [to] contain a written description of the invention, and of the manner and process of making and using it . . . to enable any person skilled in the art to which it pertains . . . to make and use the same."[65] This seemingly straightforward directive contains within it several thorny ambiguities: Does "the same" refer to the invention (in some abstract sense), the specification, or the claims? If it refers to the latter two choices, does § 112(a) require applicants to enable *all* embodiments of their inventions, or just a few? If just a few, which ones? In other words, what is the scope of the enablement inquiry?

To date, these questions have only been partially resolved. While it seems clear that the enablement doctrine operates on patents' claims, rather than some abstract concept of "the invention,"[66] the Federal Circuit has been "inconsistent or chaotic" in resolving the scope of the enablement inquiry.[67] In several cases, the court appears to have haphazardly chosen among several, irreconcilable alternatives to whether, and to what extent, enablement operates on the scope of a patent's claims.[68] In an effort of 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.[69]

The full-scope doctrine requires that a patent's specification enable the "full-scope," i.e., every limitation, of the patent's claims.[70] This has been likened to a commensurability requirement, where the patent's disclosure must be commensurate with the scope of the patent's

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[64] In *Eli Lilly*, the patent owner originally developed atomoxetine to treat urinary incontinence and depression. *Eli Lilly*, 435 F. App'x at 919-20. Clinical trials for those indications, however, failed to prove "the medicinal benefits for which [the drug] was being evaluated." *Id.* at 920.

[65] 35 U.S.C. § 102(a) (2011).

[66] *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.") (internal citations omitted); U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2164.08 (11th ed. 2013), *available at* http://www.uspto.gov/web/offices/pac/mpep/ ("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.").

[67] Collins, *supra* note 7, at 1087.

[68] *See id.* at 1088.

[69] *Id.* at 1088-89.

[70] *Id.* at 1088.

claims.[71] Under this theory, a patent that discloses anything less than all potential embodiments for its claims is invalid. *Wyeth Corp. v. Abbott Laboratories* serves as a prime example of the doctrine at its most forceful.[72] In *Wyeth*, the patentee claimed a method for treating restenosis, the narrowing of blood vessels, using "rapamycin."[73] 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.[74] 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."[75]

The single-embodiment doctrine holds just the opposite. It is satisfied where the patent specification enables a person having ordinary skill in the art to create at least a single embodiment of the claimed invention.[76] In *Spectra-Physics, Inc. v. Coherent, Inc.*, the Federal Circuit concluded that the inventor's patent on a gas laser was enabling, even though it failed to disclose one possible method for constructing it.[77] This was "not fatal" to the inventor's patent, however, 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."[78]

Lastly, the reasonableness doctrine attempts to navigate between the first two. There, a patent application satisfies the enablement requirement where there is a "'reasonable correlation' between the disclosure and the claims."[79] Practically, patent applicants or litigants have attempted to use this reasonableness doctrine in unpredictable arts where there is a wide disparity between the scope of the 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.[80] Older court cases seemed to have

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[71] *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 7, 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."); Karshtedt, *supra* note 1, at 154 ("[C]ommensurability between claim scope and disclosure . . . has long been understood to be a part of the enablement requirement of the Patent Act."); Seymore, *supra* note 26, at 634 ("The test is whether the enablement provided in the disclosure is commensurate in scope with the protection sought by the claims.").

[72] 720 F.3d 1380 (Fed. Cir. 2013).

[73] *Id.* at 1382.

[74] *Id.* at 1383.

[75] *Id.* at 1385.

[76] Collins, *supra* note 7, at 1088.

[77] 827 F.2d 1524 (Fed. Cir. 1988). 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 1530-31.

[78] *Id.* at 1533.

[79] Collins, *supra* note 7, at 1089.

[80] *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 even though the district court failed to make a finding as to the invention's "pioneer" status);

given leeway to inventors of pioneering inventions "in exchange for their outsized technological contribution to society."[81] Nonetheless, recent cases have rejected using a reasonableness doctrine as the touchstone for enablement.[82]

Although the Federal Circuit's language has recently been more forceful in adopting the full-scope doctrine as the polestar for enablement,[83] 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.[84] And scholars have criticized the rule as "unworkable."[85] According to Bernard Chao, "[t]here 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."[86] While it appears that the Federal Circuit is rapidly gravitating toward fully adopting the full-scope doctrine, lower courts, litigants, and—importantly—patent applicants remain uncertain as to the scope of the enablement inquiry.

C. Relationship with Utility

Enablement requires a patent to teach a person having ordinary skill in the art "to make and use" the invention.[87] But another patent doctrine also concerns the use of the invention: utility. Section 101 of the patent statute only allows patents on "new and useful" inventions.[88] This utility requirement has long been "assumed to be a 'low bar' to patentability or a 'nonexistent' patentability requirement."[89] It demands only that the patented invention have *some*

In re Vaeck, 947 F.2d 488, 495 (Fed. Cir. 1991) (invalidating the patent application's claims even though "[A]ppellants assert that their invention is 'pioneering,' and that this should entitle them to claims of broad scope.").

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

[82] *See* cases cited *supra* note 80.

[83] *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 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 . . . ."); Mag-Sil Corp. v. Hitachi Global Storage Techs., Inc., 687 F.3d 1377, 1381 (Fed. Cir. 2013) ("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.").

[84] *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 . . . .") (internal quotation marks omitted); *Mag-Sil*, 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.") (quoting In re Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970)) (alteration in original).

[85] Chao, *supra* note 8, at 1378.

[86] *Id.*

[87] 35 U.S.C. § 112(a) (2011).

[88] *Id.* § 101 (2011).

[89] Sean B. Seymore, *Making Patents Useful*, 98 MINN. L. REV. 1046, 1049 (2014).

beneficial use to the public and that the patent itself "be capable of achieving the [invention's] intended result."[90] Practically, these requirements set such low thresholds as to be overcome for almost all inventions except the fantastical: perpetual motion machines,[91] processes for cold fusion,[92] elixirs of eternal youth,[93] for example.

In a number of cases, however, 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.*, 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.[94] The court's opinion intimated that had the specification described jacketless injectors—at all—it would have upheld Liebel-Flarsheim's patent.[95] In other cases, however, enablement does not rise or fall on merely the *quantity* of information provided in the specification, but its *quality*. Where 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.[96] In other words, that 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.*[97] In *Process Control*, the patentee claimed a method of using a gravimetric blender, a machine important in plastic injection molding.[98] The patent's claims required the blender to perform certain calculations when feeding its grist to a later machine, a hopper.[99] Those calculations

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[90] *Id.* at 1066.

[91] Newman v. Quigg, 886 F.2d 329 (Fed. Cir. 1989).

[92] In re Swartz, 232 F.3d 862 (Fed. Cir. 2000).

[93] In re Eltgroth, 419 F.2d 918 (C.C.P.A. 1970).

[94] 481 F.3d 1371, 1375 (Fed. Cir. 2007).

[95] *See id.* ("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.").

[96] *See, e.g.*, Mag-Sil Corp. v. Hitachi Global Storage Techs., Inc., 687 F.3d 1377, 1382 (Fed. Cir. 2013) ("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 Litigation, 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 alternation in original; internal quotation marks 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.") (alterations in original).

[97] 190 F.3d at 1350.

[98] *Id.* at 1352-54.

[99] *Id.*

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.[100] 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.[101] 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.[102] The patent's inoperability therefore rendered the patent invalid because it created "a nonsensical method of operation," one which "fail[ed] to comply with the utility *and* enablement requirements of 35 U.S.C. §§ 101 and 112."[103]

But most patents with inoperability concerns don't 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.[104] 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.[105] There, the court referred to this intersection between enablement and utility as "enablement/utility."[106] And 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.[107]

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. Where 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 even a single use for its claimed invention.[108] By contrast, a patent should not fail

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[100] *Id.* at 1354.

[101] *Id.* at 1357.

[102] *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).

[103] *Id.* (emphasis added).

[104] *See* Karshtedt, *supra* note 1, at 111-13 (likening this aspect of inoperability to "unpredictable or unreliable" results); Seymore, *supra* note 89, at 1091 ("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.'").

[105] *See* Eli Lilly & Co. v. Actavis Elizabeth LLC, 435 F. App'x 917, 923-24 (Fed. Cir. 2011); notes 47-55 and accompanying text.

[106] *Eli Lilly*, 435 F. App'x at 923.

[107] *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."); *id.* at 926 ("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.'").

[108] *See* Seymore, *supra* note 89, at 1087-91 (discussing Brenner v. Manson, 383 U.S. 519 (1965)).

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. And 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.[109] Nonetheless, the Federal Circuit has been clear that "[l]ack of enablement and absence of utility are closely related grounds."[110] While an inventor's "misconceptions about scientific principles" will not often invalidate the patent,[111] this joining of enablement and utility, even for well-supported but doubtful claims, remains.

D. Later Scientific Advances

Enablement ultimately depends on a patent's claim terms.[112] To that end, courts' power to construe claim terms—to "decide[ ] what the words describing the patent holder's rights actually mean"[113]—gives courts the ability to determine whether a patent is or is not enabling. Several significant enablement opinions have turned on issues of claim construction: one proposed meaning enabled the disputed claim; the other, invalidated it.[114] The mathematical impossibility in *Process Control*, for example, only arose because the Federal Circuit construed the term "material processing rate" as equivalent to "material discharge rate."[115] Another definition of "material processing rate" would have, supposedly, cured the patent of its error in arithmetic—and made it enabling.[116]

But claim terms aren't necessarily static. Advances in science may change the meaning of claim terms long after the ink has dried on the patent document.[117] Courts interpreting claim terms with a particular scientific meaning are therefore confronted with several difficulties of

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[109] *See* Karshtedt, *supra* note 1, at 120-27 (describing this in the context of biotechnology process claims).

[110] Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1358 (Fed. Cir. 1999).

[111] *Id.* at 1359.

[112] *See supra* note 66 and accompanying text.

[113] Matthew Sag & Kurt Rohde, *Patent Reform and Differential Impact*, 8 MINN. J.L. SCI. & TECH. 1, 33 (2007).

[114] *See, e.g.*, Promega Corp. v. Life Techs. Corp., 773 F.3d 1338, 1350 (Fed. Cir. 2014) (invalidating the patent after construing "open loci set"); Wyeth Corp. v. Abbott Labs., 720 F.3d 1380, 1383 (Fed. Cir. 2013) (discussing the district court's decision to invalidate the patent for lack of enablement after broadly construing "rapamycin"); *Process Control*, 190 F.3d at 1355-56 (weighing arguments over the term "material processing rate").

[115] 190 F.3d at 1355-56.

[116] *See supra* notes 97-103 and accompanying text.

[117] *See, e.g.*, Bayer CropScience AG v. Dow AgroSciences, 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-α-1); In re Hogan, 559 F.2d 595, 608 (C.C.P.A. 1977) (reversing the examiner's rejection 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) ("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.").

time: whether to interpret those terms at the time of the patent application, or 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 practice the patent would have recognized such shifts—and, if so, when.

Schering Corp. v. Amgen Inc. presents one of the starkest examples of these interpretive difficulties.[118] In 1980, the patentee in *Schering*, Dr. 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.[119] His claims were accordingly limited to recombinant molecules of "interferon" and their attendant DNA sequences.[120] 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 interferon alpha (IFN-α), beta (IFN- β), and gamma (IFN-γ). Each of these, in turn, was comprised of various subtypes, IFN-α-1, IFN-α-2, and so on.[121] Now understanding that his recombinant protein referred to a single one of these subtypes—IFN-α-1—Weissmann amended his patent's claims, changing "interferon" to "IFN-α-1."[122] 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.[123] 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-α-1 meant *only* IFN-α-1, Schering recognized that it could not prevail at trial.[124]

Schering highlights several of the difficulties of assessing enablement when courts confront claim terms with evolving scientific meanings.[125] In these evolving meaning cases, both the district and appellate courts need to determine whether there is a salient difference between the disputed claim term—as used in the patent—and 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-α-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

[118] 222 F.3d at 1347.

[119] *Id.* at 1349-50; *see also* STEPHEN S. HALL, A COMMOTION IN THE BLOOD 131-58 (1997) (discussing the history of the discovery of interferon).

[120] *Schering*, 222 F.3d at 1350.

[121] *Id.* at 1352; HALL, *supra* note 119 at 178-208.

[122] *Schering*, 222 F.3d at 1352.

[123] *Id.*

[124] *Id.* at 1349.

[125] *See id.* at 1353 ("The scientific meaning of 'IFN-α' evolved with new discoveries.").

invention the inventor possessed at the time of filing,[126] an analysis criticized by Robin Feldman as future "assumptions about how far a particular invention can reach."[127]

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.[128] Weissmann's amendments in *Schering* were just that—amendments—that he made during the prosecution of the patent, and was therefore bound to for the court's ultimate infringement analysis.[129] In another case, *Bayer CropScience AG v. Dow AgroSciences LLC*, the patentee had not been so swift.[130] There, the parties disputed when the patentees became aware that their use of the term "monooxygenase" had been essentially proven incorrect by later research.[131] The Federal Circuit ultimately held this lapse against the patent owner and affirmed the district court's invalidation of the patent.[132] To resolve this apparent dichotomy, Mark A. Lemley has strongly argued to fix these inquiries—and the meaning of claim terms—on the date of the patent application.[133]

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.[134]

Schering potentially suffered from just these sort of problems: that the changing understanding of interferons would have meant that "IFN-α-1" take on different meanings for different defendants, or that the patent could have withstood validity challenges on some days, but not

[126] *See* Holbrook, *supra* note 26, at 132 (discussing the intersection of enablement and possession).

[127] Feldman, *supra* note 7, at 25.

[128] 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 (2011). 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. Laura A. Bauer, *Modified Reissue Practice*, 8 FED. CIRCUIT B.J. 193, 198 (1999).

[129] 222 F.3d at 1352-53.

[130] 728 F.3d 1324, 1328-29 (Fed. Cir. 2013).

[131] *Id.*

[132] *Id.* at 1332.

[133] Lemley, *supra* note 7, at 115-16.

[134] *Id.* at 116.

others.[135] Cases like *Schering* ultimately show that science runs the risk of running away with the enablement inquiry.

II. SCIENTIFIC IRREPRODUCIBILITY

A. The Importance of Reproducibility in Science

In theory, science proceeds by hypothesis testing: by generating hypotheses about natural phenomena and subjecting those hypotheses to rigorous testing.[136] 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 other peer scientists, of the testing design, the conduct of the experiments, and the conclusions drawn by the original investigator.[137] Once a report survives peer review—arguably the superlative standard in scientific publishing[138]—other scientists can then adopt and internalize the report's findings.[139] 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.[140]

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[135] Regarding the former contention, that IFN-α-1 could have taken on different meanings for different defendants, this was, in substance, Schering's infringement argument at trial: that IFN-α-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. REPORTER, Apr. 5, 1999 (discussing Schering's strategy, and the district court's dismissal of Amgen's invalidity counterclaim).

[136] POPPER, *supra* note 1, at 9 ("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—stands up to the demands of the practice, whether raised purely by scientific experiments, or by practical technological applications.").

[137] ADIL E. SHAMOO & DAVID B. RESNIK, RESPONSIBLE CONDUCT OF RESEARCH 69-70 (2d ed. 2009) (discussing the components of the typical peer review process).

[138] 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.").

[139] Note, Effie J. Chan, *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.").

[140] *See* Eisenberg, *supra* note 26, at 1055 ("[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.").

In reality, however, science does not ossify around past publications.[141] 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.[142] In that spirit, scientists often attempt to replicate each other's experiments—both to generate hypotheses of their own, but also as a further check on the peer review process.[143] The success, or failure, of these attempts to replicate prior results are often measured as a study's "reproducibility": whether a published experiment is, in fact, reproducible by an independent group of researchers.[144] If a research result is not reproducible—if other investigators can't 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.[145] In this way, science is largely self-correcting: "errors are systematically criticized and fairly often, in time, corrected."[146]

There are endless ways for scientific experiments to fail. And, equally, 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.[147] 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.[148] 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.[149] Statistical reproducibility, by contrast, concerns whether a experiment can be repeated with the same degree of statistical certainty as its predecessor, or

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[141] *See* LARRY LAUDAN, PROGRESS AND ITS PROBLEMS 25 (1977) ("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.").

[142] *See* Sheila Jasanoff, *Technologies of Humility*, 450 NATURE 33, 33 (2007) ("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.").

[143] *See* COLLINS, *supra* note 1, at 29-50 (discussing the role of replication in scientific practice). *But see* Eisenberg, *supra* note 26, at 1049-51 (describing the lack of practical incentives for replication studies).

[144] *See* Victoria Stodden, *Reproducibility*, in THIS IDEA MUST DIE 529 (John Brockman ed. 2015) (discussing reproducibility).

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

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

[147] Victoria Stodden, *Reproducibility*, in THIS IDEA MUST DIE 529 (John Brockman ed. 2015).

[148] *Id.*

[149] ROBERT D. PURRINGTON, THE FIRST PROFESSIONAL SCIENTIST: ROBERT HOOKE AND THE ROYAL SOCIETY OF LONDON 48-50 (describing the resolution of Huygen'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 147, at 529.

whether the conclusions of the original study's authors were statistically sound.[150] Errors in the application of certain statistical methods, data collection, and sample sizes, for example, can generate statistically irreproducible results.[151] 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."[152] As an increasing number of scientific disciplines rely on code to test hypotheses and generate results—meteorology, astronomy, molecular biology—and understanding and being able to use that code has become critical in ascertaining whether previously published results are, in fact, reproducible.[153]

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."[154] It is "the touchstone of the scientific method and one of the strongest norms of the research community."[155]

B. Recent Concerns Over Irreproducibility

Recently, several researchers—including the Director of the NIH, Francis S. Collins—voiced their concerns that many peer reviewed, published scientific studies were irreproducible or, at the least, not replicable. [156] While outright fraud was extremely rare—only 12 cases in 2011 out of thousands and thousands performed[157]—Collins and Lawrence A. Tabak, the Principal Deputy Director of the NIH attributed this crisis in reproducibility to "a complex array of other factors," such as

> poor training of researchers in experimental design; increased emphasis on making provocative statements rather than presenting 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—

[150] Stodden, *supra* note 147, at 529.

[151] Stodden, *supra* note 1, at 2-4.

[152] *Id.* at 2.

[153] The Yale Law School Roundtable on Data and Code Sharing, *Reproducible Research*, COMPUT. SCI. ENG'R, Sept./Oct. 2010, 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.") (internal citations omitted).

[154] SHAMOO & RESNIK, *supra* note 137, at 51.

[155] Karshtedt, *supra* note 1, at 109.

[156] *E.g.*, Collins & Tabak, *supra* note 3, at 612; Downing et al., *supra* note 3, at 368; Easton et al., *supra* note 3, at 2243; Ioannidis, *Research Findings*, *supra* note 3, at 696; Ioannidis, *Contradicted Effects*, *supra* note 3, at 218; Ioannidis et al., *Replication Validity*, *supra* note 3, at 306; Lau, Ioannidis, & Schmid, *supra* note 3, at 123; Leek & Peng, *supra* note 3, at 612; Randall J. LeVeque, Ian M. Mitchell, & Victoria Stodden, *Reproducible Research for Scientific Computing: Tools and Strategies for Changing the Culture*, COMPUT. SCI. ENG'R 13 (July/Aug. 2012); Light & Lexchin, *supra* note 3, at H2068; Stodden, *supra* note 1, at 1; The Yale Law School Roundtable on Data and Code Sharing, *supra* note 153, at 8.

[157] Collins & Tabak, *supra* note 3, at 612.

> and withhold details from publication or describe them only vaguely to retain a competitive edge.[158]

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 claimed that "false findings may be the majority or even the vast majority of published research claims."[159] 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.[160] The article developed metrics for assessing a given study's "pre-study odds"—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.[161] 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.[162] After assessing various types of studies, Ioannidis concluded that, generally, "a PPV exceeding 50% is quite difficult to get."[163] In some types of studies, such as "discovery-oriented exploratory research with massive testing," Ioannidis calculated PPV to be 0.1%. In other words, each result in such a study is likely to be *irreproducible 99.9%* of the time.[164]

Some of the biases studied by Ioannidis focused on the tools of statistical inquiry themselves.[165] Researchers' reliance on one such tool, statistical significance (*p*), have raised some particularly thorny issues of reproducibility. A 1998 study criticized the use of *p*-values in meta-analyses of clinical trials.[166] The measurement failed to take into account the heterogeneity of multiple studies, or the studies' differences in sample sizes, or certain random effects present in each study.[167] 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.[168] 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.[169] And at its most extreme, researchers' reliance on *p*-values had the effect of creating competing, contradicted studies—later researching findings that came to

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[158] *Id.*

[159] Ioannidis, *Research Findings*, *supra* note 3, at 696.

[160] *Id.*

[161] *Id.*

[162] *Id.* at 700.

[163] *Id.* at 699.

[164] *Id.* at 700.

[165] *Id.* at 696-97 (discussing the statistical measurements of error, power, and significance); *see also* Stodden, *supra* note 1, at 1 (discussing statistical irreproducibility).

[166] Lau, Ioannidis, & Schmid, *supra* note 3, at 125.

[167] *Id*. at 124-26.

[168] *Id.* at 125.

[169] Regina Nuzzo, *Statistical Errors*, 506 NATURE 150, 150 (2014) (describing one such instance).

the *opposite* conclusions of their predecessors.[170] Even the Supreme Court—a court of law, not of math—has cast doubt on its importance. In *Matrixx Initiatives, Inc. v. Siracusano*, the Court allowed shareholders of a drug manufacturer to pursue their securities claims against the company concerning its alleged misrepresentation of its drugs' side effects.[171] 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."[172] "This premise is flawed," concluded the Court, for many of the same reasons researchers have come to criticize the measurement.[173] Stephen T. Ziliak and Deirdre N. McCloskey have controversially derided this reliance on *p*-values as "a cult of *p*."[174]

Irreproducibility also stems from what Collins and Tabak's dub the "secret sauce," where researchers "withhold details from publication or describe them only vaguely to retain a competitive edge."[175] One medical diagnostics company, Theranos, has essentially banked on this asymmetry, protecting its methods and results as trade secrets rather subjecting its products to peer review or disclosing them in patents.[176] The FDA recently cleared one Theranos product—a $9 blood test for herpes—for sale.[177] But without public access to such data, "stealth research" like Theranos's has little hope of having "its methods and technologies scrutinized and validated by independent scientists."[178]

In other instances, reproducibility appears impossible because researchers simply refuse to adequately disclose their methods in obtaining computational results.[179] In the precision medicine context—where scientists attempt to link individual genetic variations to disease—clinicians often rely on "opaque computational models to make decisions related to health care," what W. Nicholson Price II calls "black-box medicine."[180] "Secrecy, however, is a problematic

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[170] *See* Ioannidis, *Contradicted Effects*, *supra* note 3, at 223-26 (discussing the factors that contribute to contradicted findings).

[171] 131 S. Ct. 1309 (2011).

[172] *Id.* at 1319 ("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.'").

[173] *See id.* at 1319-20 (discussing the impossibility of obtaining statistically significant measurements for small samples, alternatives to significance for expert testimony on causation, and the FDA's use of significance—or lack thereof—for post-market surveillance of approved drugs).

[174] STEPHEN T. ZILIAK & DEIRDRE N. MCCLOSKEY, THE CULT OF STATISTICAL SIGNIFICANCE 9 (2008).

[175] Collins & Tabak, *supra* note 3, at 612.

[176] John P.A. Ioannidis, *Stealth Research: Is Biomedical Innovation Happening Outside the Peer-Reviewed Literature?*, 313 JAMA 663, 663 (2015).

[177] Letter from Sally A. Hojvat, Director, Division of Microbial Sciences, FDA, to Brad Arington, Associate Director, Theranos, Inc., July 2, 2015, *available at* https://s3.amazonaws.com/s3.documentcloud.org/documents/2157669/k143236-letter-se-final-corrected-2015-07-02.pdf.

[178] Ioannidis, *supra* note 176, at 664.

[179] Victoria Stodden, *Trust Your Science? Open Your Data and Code*, AMSTAT NEWS, July 2011, at 21; The Yale Law School Roundtable on Data and Code Sharing, *supra* note 153, at 8.

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

incentive for the datasets underpinning the development of black-box medicine and makes method validation impossible."[181] Without external validation, any scientific finding using these models simply "retains whatever biases or errors may have created problems in the first place."[182] And disconcertingly, "the FDA currently lacks the expertise and resources to independently replicate a company's algorithmic results."[183]

Even where 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 several 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.[184] 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.[185] Secrecy of this sort is simply "not independently verifiable or replicable."[186] 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.[187]

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 irreproducible studies.[188] 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.[189] Improper use or characterization of antibodies can cause them to react with unintended molecules, resulting in both false positive and false negative results.[190] In other cases, manufacturing variability within a single batch of antibodies can yield different results across different conditions.[191] And even using "good" antibodies, slight changes in experimental

[181] *Id.* at 447.

[182] *Id.* at 441.

[183] *Id.* at 442.

[184] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

[185] 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).

[186] *Id.* at 635.

[187] Dan L. Burk, *Patents as Data Aggregators in Personalized Medicine*, B.U. J. SCI. TECH. L. (forthcoming 2015), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2597525.

[188] 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?WT.mc_id=TWT_NatureNews ("Overall, the team found that poor materials made the largest contribution to reproducibility problems, at 36% . . . .").

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

[190] *Id.* at 276.

[191] *Id.*

conditions can move the needle on certain results.[192] 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."[193]

C. Irreproducibility in Clinical Trials

While irreproducibility has the potential to threaten all areas of the scientific endeavor, it seems particularly poignant in biomedical research.[194] News reports recently focused on one study that claimed that "[s]cientists in the United States spend $28 billion each year on basic biomedical research that cannot be repeated successfully."[195] The study examined other reports of irreproducibility in an attempt to characterize and quantify their causes, finding that roughly 50% of all preclinical cancer studies contained at least one irreproducible result.[196] Given that the U.S. spends roughly $56 billion each year on such studies, this amounted, in the authors' view, to close to $28 billion of waste.[197] 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."[198] 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."[199] 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, tenure pressures.[200]

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

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[192] *Id.*

[193] *Id.* at 274.

[194] Baker, *supra* note 188, at 1 ("Scientists in the United States spend $28 billion each year on basic biomedical research that cannot be repeated successfully."); Baker, *supra* note 165, at 274 (examining 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"); Collins & Tabak, *supra* note 132, 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 3, 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."); Jocelyn Kaiser, *Cancer Reproducibility Effort Faces Backlash*, SCIENCE NEWS, June 25, 2015, http://news.sciencemag.org/biology/2015/06/feature-cancer-reproducibility-effort-faces-backlash ("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.").

[195] Baker, *supra* note 188, at 1.

[196] Leonard P. Freedman, Iain M. Cockburn, & Timothy S. Simcoe, *The Economics of Reproducibility in Preclinical Research*, 13 PLOS BIOLOGY e1002165, e1002165 (2015).

[197] *Id.* at e1002167.

[198] Baker, *supra* note 165, at 275.

[199] Ioannidis, *Research Findings*, *supra* note 3, at 698.

[200] Alberts et al., *supra* note 145, at 1421.

the ills found by Ioannidis as giving rise to irreproducible results, including small sample sizes, small effects, a larger number of tested variables, increasing flexibility in design, a greater potential for conflicts of interest, and a higher quotient of competitive popularity.[201] One analysis of forty-nine "highly cited original clinical research studies" found that follow-on studies in seven—16%—wholly contradicted their earlier study's findings.[202] In one particularly egregious example, a 1991 clinical trial claimed that post-menopausal women receiving hormone replacement therapy were 44% less susceptible to coronary artery disease.[203] A 2002 follow-up trial concluded, much to the contrary, that hormone replacement therapy was responsible for a 29% *increase* in coronary artery disease.[204] (Perhaps unsurprisingly, this seventy-three percentage point swing resulted in a substantial products-liability lawsuit against the therapy's manufacturer, Wyeth.[205]) 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 effects reported by the previous study were, in fact, substantially diminished. 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.[206] In all, eighteen of the forty-nine clinical trials, or 36.7%, could not be reproduced.[207] Perhaps equally concerning is that, to date, eleven of the original forty-nine clinical trials have yet to be challenged in any way.[208]

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.[209] An exhaustive 2014 study that revisited the clinical trial data for all new drugs approved by the FDA from 2005 to 2012 concluded that "the quality of clinical trial evidence used by the FDA to make approval decisions varied widely across indications."[210] Some of this flexibility is the product of necessity; "[a] perfect gold standard is not possible in clinical research."[211] Some may be even "be warranted given the limited number

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[201] Ioannidis, *Research Findings*, *supra* note 3, at 697-98.

[202] Ioannidis, *Contradicted Effects*, *supra* note 3, at 218.

[203] *See id.* at 223 (discussing Meir J. Stampfer et al., *Post-Menopausal Estrogen Therapy and Cardiovascular Disease: Ten-Year Follow-Up From The Nurses' Health Study*, 325 NEW ENGL. J. MED. 756 (1991)).

[204] Ioannidis, *Contradicted Effects*, *supra* note 3, at 223 (discussing Writing Group 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 JAMA 321 (2002)).

[205] *See generally* Tobias Millrood, *The Rise and Fall of Hormone Therapy*, TRIAL, August 2003, at 42.

[206] Ioannidis, *Contradicted Effects*, *supra* note 3, at 222.

[207] This can be calculated by adding together the number of clinical trials where later research has demonstrated a contradicted effect (7), no effect (4), or a substantially diminished effect (7).

[208] Ioannidis, *Contradicted Effects*, *supra* note 3, at 218.

[209] 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).

[210] Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012*, 311 JAMA 368 (2014).

[211] Ioannidis, *Contradicted Effects*, *supra* note 3, at 224.

of effective therapies and the poor prognosis associated with [diseases like] cancer."[212] Nonetheless, several of the measurements allowed by the FDA to prove efficacy are particularly suspect, including surrogate end points—measures of disease progression, like the size of patients' tumors—as opposed to clinical end points—whether patients ultimately survive in spite of or die from their disease.[213] "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,"[214] i.e., that such results are not, in fact, real.

Even clinical trials that do measure survival times often suffer from low effect sizes, a hallmark of irreproducible results.[215] In the cancer context, clinical trial subjects of seventy-one solid tumor drugs approved by the FDA 2002 to 2014 improved their lifespan, at median, by only two-and-a-half months.[216] A similar subset of drugs approved by the European Medicines Agency found only a one-and-a-half month gain.[217] Attempts to replicate even successful studies have been met with skepticism if not outright backlash.[218] In a similar vein, genetic association studies—studies attempting to link an individual's risk of developing a genetic disease, such as cancer, with a particular genetic variation—also suffer from low effect sizes. A 2001 study of thirty-six genetic disease associations found, "Often genetic associations of disease are of modest magnitude . . . and single studies are underpowered to detect them."[219] 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.[220] Another study of commercially available multi-gene diagnostic tests cast doubt on the

[212] Downing et al., *supra* note 210, at 373.

[213] *Id.* at 374.

[214] *Id.*

[215] Ioannidis, *Research Findings*, *supra* note 3, at 697 ("The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.").

[216] Light & Lexchin, *supra* note 3, 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.").

[217] *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.").

[218] *See* Kaiser, *supra* note 194, at 1 (describing such efforts).

[219] Ioannidis et al., *Replication Validity*, *supra* note 132, at 308.

[220] *Id.* at 307 ("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.").

linkage between over a dozen genes analyzed by such services and cancer risk.[221] Of the eleven commercial tests analyzed, every one tested for at least one such dubious genetic variant.[222]

And yet, even where clinical trials meet the "gold standard" in terms of experimental design and predictive power,[223] 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."[224] Furthermore, even the gold standard is, itself, "inadequate because its statistical framework requires no particular level of efficacy."[225] 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."[226] 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."[227]

Ultimately, quantifying the amount of irreproducibility in clinical trials may simply be impossible. Not every clinical trial is validated with its own follow-on study, which, in any event, may suffer from its own deficiencies.[228] Clinical trials—and even follow-on trials—are often conducted under the guise of FDA regulations, which have an instrumental rather than investigatory bent.[229] And new drug applicants can often keep their most damning negative results confidential under the FDA's own regulations. [230] As a result, "[n]on-commercial researchers deprived of the means to independently re-analyze raw data cannot easily verify or refute product sponsors' safety and efficacy claims."[231]

III. IRREPRODUCIBILITY AND PATENTED DRUGS

A. Incentives for Irreproducible Drug Patents

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 potentially

[221] *See* Easton et al., *supra* note 3, at 12.

[222] *Id.* at 2.

[223] Darrow, *supra* note 209, at 2090 (enumerating several "gold standards" in clinical trials: "randomization, double-blind administration, and placebo-control").

[224] *Id.* at 2095.

[225] *Id.*

[226] *Id.* at 2112.

[227] *Id.* at 2076.

[228] Ioannidis, *Contradicted Effects*, *supra* note 3, at 218.

[229] Darrow, *supra* note 209, at 2075-76.

[230] Eisenberg, *supra* note 19, at 382-83.

[231] LAAKMANN, *supra* note 20, at 20.

applicable doctrine, enablement, appears ill-suited to take irreproducibility into account: it is unclear whether any post-application evidence can be introduced to invalidate patents based on irreproducible data,[232] let alone general scientific advances that call into question prior assumptions about a particular field.[233] Enablement's relationship with the scope of patents' claims—and, consequently, which aspects of the patent may or not may be irreproducible—remains stubbornly unsettled.[234] And the doctrine remains confusingly mixed up with operability, a single concern in the broader concept of irreproducibility.[235] In this sense, even though irreproducible patents can be thought of as *dis*enabling, they remain entitled, as with other patents, to an ongoing presumption of validity.[236]

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.[237] 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."[238]

To avoid this, drug developers often rely on early, preclinical studies to bolster their patents.[239] 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 employers[240]—all hallmarks of irreproducibility.[241] Nonetheless, patent applications rooted in

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[232] *See supra* Part I.A.

[233] *See supra* Part I.D.

[234] *See supra* Part I.B.

[235] *See supra* Part I.C (discussing the differences among empirical, statistical, and computational reproducibility).

[236] *See* 35 U.S.C. § 282 ("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).

[237] Hilton Davis Chem. Co. v. Warner-Jenkinson Co., 62 F.3d 1512, 1536 (Fed. Cir. 1995) (en banc) (per curiam) (Newman, J., concurring), *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 19, 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 40, at 161-62 (quoting *Hilton Davis* and discussing this in the context of pharmaceutical development); *see also* Cotropia, *supra* note 16, at 93-96 (describing the negatives of early patent filing).

[238] Seymore, *supra* note 40, at 162.

[239] *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 . . . .").

[240] *See, e.g.*, Katherine S. Button et al., *Power Failure: Why Small Sample Size Undermines the Reliability of Neuroscience*, 14 NATURE REV. NEUROSCI. 365, 373 (2013) (describing these factors as "the root of the recent replication failures in the preclinical literature"); 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 et al.,

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,[242] a standard that can be met even with animal testing or *in vitro* analyses.[243] 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."[244]

The early, easy patenting of drugs encourages patent applicants to adopt several troublesome strategies at the patent office. Patentees of new drugs, already encouraged to claim broadly,[245] often draft their claims as directed to methods of treating broader classifications of diseases than any preclinical data warrants.[246] U.S. Patent No. 8,652,776, for 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.[247] 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.[248] 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

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Pharmacological Intervention Studies Using Mouse Models of the Inflammatory Bowel Diseases: Translating Preclinical Data into New Drug Therapies, 17 INFLAMMATORY BOWEL DISEASE 1229 (2011) (criticizing preclinical studies of inflammatory bowel disease in mice); Emily Sena et al., *How Can We Improve the Pre-Clinical Development of Drugs for Stroke?*, 30 TRENDS NEUROSCI. 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).

[241] Ioannidis, *Research Findings*, *supra* note 3, at 697-98.

[242] U.S. PATENT AND TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2107.03 (Mar. 2014).

[243] *Id.*

[244] *Id.* (emphases added).

[245] Chao, *supra* note 8, 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.").

[246] *See* Budish, Roin, & Williams, *supra* note 4, 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 7, at 13 (describing this in the context of antibody therapeutics); Eileen M. Kane, *Patent-Mediated Standards in Genetic Testing*, 2008 UTAH L. REV. 835, 859 (2008) ("[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 180, at 445 (weighing similar incentives in the context of diagnostic algorithms); Roin, *supra* note 239, at 522-26 (describing this practice's effect on patentability); Sean B. Seymore, *Patently Impossible*, 64 VAND. L. REV. 1491, 1517-23 (discussing the history of patents on cancer treatments).

[247] U.S. Patent No. 8,652,776, col. 15, ll. 60-61 (filed Sept. 10, 2008).

[248] Seymore, *supra* note 40, at 145-46 ("A generic claim uses structural formulas8 or functional language to cover embodiments that share a common attribute. This style of claiming pervades the chemical and pharmaceutical arts, and affords the broadest claim scope under the patent laws. Indeed, a single generic claim can easily encompass millions, billions, or novemdecillions of compounds."). *But see* Wyeth Corp. v. Abbott Labs., 720 F.3d 1380, 1385 (Fed. Cir. 2013) (rejecting this approach).

research. Rather, patentees are encouraged to say little about the methodology of any supporting studies and then wait for an examiner's response.[249] 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—is of much greater consequence than whether the studies are, in any sense, reproducible.[250] Lastly, patentees may also be encouraged to draft ambiguous claims in the hope of retaining textual flexibility as developmental research on the studied drug's progresses.[251] 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.[252] 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.

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,[253] the character of irreproducibility in drug patents is similarly varied: patents based on contradicted preclinical or clinical trials; patents based on unreplicated data; patents covering a broader indication or target population than warranted; and patents based with such a small effect as to be doubtful. Prempro, Xigris, Plavix, and Avastin each 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.[254] Clinicians attribute the onset of these illnesses, at least in part, to the decrease in hormone production following menopause.[255] Hormone replacement therapy (HRT)—small doses of hormones intended to mimic a pre-menopausal state—were consequently viewed as a logical treatment.[256]

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[249] Lemley, *supra* note 7, at 117 (discussing the patentee's strategy of "wearing down the examiner" in *Chiron v. Genentech*, 266 F. Supp. 2d 1172 (E.D. Cal. 2002)).

[250] 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).

[251] *See* Chao, *supra* note 8, at 1372-75 (discussing the incentives behind unclear claiming).

[252] *See* Collins, *supra* note 7, at 1090-92 (discussing the expansion of claim language with time to cover after-arising technology).

[253] *See supra* Part I.C (discussing the differences among empirical, statistical, and computational reproducibility).

[254] Millrood, *supra* note 205, at 42 (discussing Writing Group for the Women's Health Initiative Investigators, *supra* note 204, at 321).

[255] Millrood, *supra* note 205, at 42 (citing Bernardine Healy, *The Mysteries of Menopause*, U.S. NEWS & WORLD REP., Nov. 18, 2002, at 39, 41).

[256] *See* Millrood, *supra* note 205, at 42 (examining the history of hormone therapy).

Beginning in the 1980s, numerous companies began to manufacture, market—and patent—various types of HRTs as treatments to ameliorate menopause-related illnesses.[257] Wyeth Pharmaceuticals, the largest HRT manufacturer, sold several different therapies: Premarin, Prempro, and Premphase.[258] Unsurprisingly, Wyeth also sought to protect each of these drugs with various patents. U.S. Patent No. RE36,247, for example, covered Prempro,[259] which claimed "[a] method of hormonally treating menopausal or post-menopausal disorders in a woman,"[260] including "dosages and duration of treatment . . . sufficient to prevent or retard changes in blood lipids which might otherwise predispose the woman to cardiovascular disease."[261] 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.[262] Despite these concerns, by 2001, Prempro's annual sales topped $733 million,[263] its success much indebted to Wyeth's aggressive marketing of the drug's cardiovascular benefit.[264]

The rapid rise of hormone replacement therapy—and questions concerning its actual benefit—led the NIH to support large-scale randomized trials of HRTs.[265] One such trial, a 2002 study of various HRTs—the Women's Health Initiative Study—came to the opposite conclusion of Prempro's patent, and an earlier, major, 1991 observational trial.[266] Rather than *preventing* the incidence of cardiovascular disease in menopausal women, HRTs, including Prempro, "significantly *increased* the relative risk of coronary events by 29% among postmenopausal women."[267] A further, follow-up, randomized trial—the Heart and Estrogen/Progestin Replacement Study—came to a similar damning conclusion.[268] The results of these studies

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

[258] *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 (2006).

[259] *See* TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53 FOR NDA 20-527 (Apr. 13, 2000), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/20-527S017_Prempro%20&%20Premphase_AdminCorres_P1.pdf, at 2 [hereinafter PATENT INFORMATION].

[260] U.S. Patent No. RE36,247, col. 10, ll. 22-23 (filed Oct. 13, 1995).

[261] *Id.*, col. 16, ll. 7-9.

[262] *See id.*, col. 7:57–9:17 (describing this study and its follow-up).

[263] Millrood, *supra* note 205, at 42 n.3.

[264] *See id.* at 43 (describing Wyeth's marketing of its drugs).

[265] *See* Ioannidis, *Contradicted Effects*, *supra* note 3, at 223.

[266] *See id.* (discussing the Women's Health Initiative Study and the Nurses' Health Study).

[267] *Id.*; *see also* Writing Group for the Women's Health Initiative Investigators, *supra* note 204, at 321.

[268] Ioannidis, *Contradicted Effects*, *supra* note 3, at 223 (discussing Stephen Hulley et al., *Heart and Estrogen/Progestin Replacement Study (HERS) Research Group Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease In Postmenopausal Women*, 280 JAMA 605 (1998)).

spawned countless lawsuits against Wyeth and led, ultimately, to Wyeth's successor, Pfizer, paying $896 million in settlements.[269]

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.[270] In that sense, a person having ordinary skill in the medical art could simply not "make and use" the invention.[271] 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 encompasses a full-scope, single-embodiment, or reasonableness analysis.[272] 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."[273]

Yet, enablement's focus on *pre*-application evidence,[274] even in the face of contradictory scientific advances,[275] 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.*, suggests otherwise.[276] In *Gilead*, the plaintiffs sought discovery of the defendants' Abbreviated New Drug Application with the FDA, in order to combat the defendants' arguments concerning the asserted patent's lack of enablement.[277] The district court refused on the grounds that "everything that the Plaintiffs would need to defend against a claim of invalidity through enablement theory is within the four corners of the Plaintiffs' own patent."[278] 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,[279] and it quietly expired on May 2, 2006.[280]

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[269] Jef Feeley, *Pfizer Paid $896 Million in Prempro Settlements*, BLOOMBERG BUSINESS, June 19, 2012, http://www.bloomberg.com/news/articles/2012-06-19/pfizer-paid-896-million-in-prempro-accords-filing-shows-1-.

[270] *See* U.S. Patent No. RE36,247, col. 16, ll. 7-9 (filed Oct. 13, 1995).

[271] *See* 35 U.S.C. § 112(a).

[272] *See* Collins, *supra* note 7, at 1087 (describing the differences in these doctrines).

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

[274] *See supra* Part I.A.

[275] *See supra* Part I.D.

[276] Docket No. 190, No. 1:14-cv-99 (N.D. W. Va. July 1, 2015).

[277] *Id.* at 2-4.

[278] *Id.* at 4.

[279] 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. Am. Home Prods. Corp. v. Novo Nordisk Pharma., Inc., Case No. 3:99-cv-3162, Docket No. 24 (D.N.J. June 23, 2000).

[280] *See* PATENT INFORMATION, *supra* note 259, at 2.

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,[281] and voluntarily withdrawn by its manufacturer, Eli Lilly & Co., in 2011,[282] serves as a prime example.

Sepsis is a general inflammatory response to an infection.[283] In severe cases, sepsis can cause the coagulation of blood and the resulting creation of circulating blood clots.[284] 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% of all recorded deaths.[285] The inflammation pathway giving rise to sepsis is complex—isolating the proteins responsible still baffles scientists[286]—but one protein involved, activated protein C (APC), had long been hypothesized to play a role in inhibiting fatal coagulation and clotting.[287]

In 2001, Eli Lilly & Co. received FDA approval for a recombinant version of APC, marketed as Xigris, for the treatment of severe sepsis.[288] 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.[289] 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 for 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.[290] 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.[291] As for a human trial, the patent only proposes a protocol for conducting one.[292]

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[281] *See* FDA, FDA CLINICAL REVIEW DROTRECOGIN ALFA (ACTIVATED) (Nov. 21, 2001), *available at* http://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113438.pdf.

[282] ELI LILLY & CO., LILLY ANNOUNCES WITHDRAWAL OF XIGRIS® FOLLOWING RECENT CLINICAL TRIAL RESULTS (Oct. 25, 2011), *available at* https://investor.lilly.com/releasedetail.cfm?releaseid=617602.

[283] FDA, *supra* note 281, at 9.

[284] *Id.*

[285] *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 R28 (2009).

[286] Charalampos Pierrakos & Jean-Louis Vincent, *Sepsis Biomarkers: A Review*, 14 CRITICAL CARE R15 (2010).

[287] FDA, *supra* note 281, at 9.

[288] *See id.* at 1.

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

[290] U.S. Patent No. 6,344,197, col. 10, ll. 39-43.

[291] *Id.*, col. 2, ll. 19-36.

[292] *Id.*, col. 10, ll. 6-37.

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.”[293] 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.[294] 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.[295] In comparison to the ’197 patent’s data, the results predicating the ’296 patent seemed promising. And that promise—as well as the ’197 and ’296 patents, and others—led Eli Lilly to aggressively market 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.”[296] As a result of this marketing, Xigris garnered Eli Lilly over $100 million per year in sales.[297]

This promise was not to last, however. The FDA conditioned its approval of Xigris on a larger follow-up study that enrolled hundreds of patients, rather than dozens.[298] 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.”[299] 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,[300] Eli Lilly subsequently withdrew its drug from the FDA’s marketing roles.[301]

And yet—to date—the Xigris patents live on. Neither the ’197 nor the ’296 patent appear to ever 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 in order 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.[302]

But the complexities in enablement doctrine itself complicates this analysis. First, given the conflicting data on the efficacy of Xigris, it is unclear whether the patents are disenabling for

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[293] U.S. Patent No. 6,489,296, col. 15, ll. 14-17.

[294] *Id.*, col. 13, l. 48 – col. 15, l. 49.

[295] *Id.*, col. 14, ll. 6-10.

[296] Judy Stone, *Lilly’s Shocker, or the Post-Marketing Blues*, SCI. AM., Nov. 2, 2011, http://blogs.scientificamerican.com/guest-blog/lillys-shocker-or-the-post-marketing-blues/.

[297] Antonio Regalado, *To Sell Pricey Drug, Eli Lilly Fuels a Debate Over Rationing*, WALL ST. J., Sept. 18, 2003.

[298] *See* Stone, *supra* note 296.

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

[300] *See* Regalado, *supra* note 297.

[301] ELI LILLY & CO, *supra* note 282.

[302] *See supra* notes 30-34 and accompanying text (discussing “undue experimentation” in enablement).

the entire scope of their claims, or just some part of them.[303] Xigris may, in fact, work for some patients in some circumstances (although this is doubtful).[304] In that sense, whether the Xigris patents are enabling turns on resolving the scope of 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,"[305] or whether they merely require an improbable *but permissible* method of operation. Lastly, while 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 post-application evidence can be introduced to invalidate a patent for lack of enablement does not, in fact, resolve the enablement inquiry.[306] Rather, it also raises questions of which post-application 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: Narrower Indication

Some pharmaceutical patents are irreproducible not due to the overall truth or falsity of their claims but for reasons having to 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," i.e., heart attacks, strokes, and vascular death, in patients previously diagnosed with atherosclerosis.[307] The drug itself—clopidogrel bisulfate—acts on one particular protein, $P2Y_{12}$, to block its role in platelet aggregation, one of the steps in harmful blood clotting.[308] Since its approval in 1997, Sanofi, the French pharmaceutical giant, has manufactured Plavix, and sold it, globally, for approximately $9.3 billion per year.[309] Naturally, Sanofi was granted a patent on the method of using Plavix to "prevent the occurrence of a secondary ischemic event."[310]

Prior to Plavix exerting its effect on $P2Y_{12}$, however, it must be metabolized into several intermediary chemicals.[311] 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

[303] *See supra* Part I.B (discussing this difficulty in enablement doctrine).

[304] *See* Ranieri et al., *supra* note 299, at 2062 ("The lack of benefit was consistent across predefined subgroups.").

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

[306] *See supra* Part I.A.

[307] FDA, CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW [Plavix] 2 (Oct. 15. 1997), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20839_Plavix_clinphrmr_P1.pdf.

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

[309] 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/.

[310] U.S. Patent No. 5,576,328, col. 6, ll. 60-62 (filed Jan. 31, 1994).

[311] Shah & Shah, *supra* note 308, at 702 ("Clopidogrel ispharmacologically inactive and requires activation to its pharmacologically active thiol metabolite that binds irreversibly to the $P2Y_{12}$ receptors on platelets.")

responsible for drug metabolism.[312] One such gene, *CYP2C19*, plays an outsized role in responsiveness to Plavix.[313] Plavix patients with dysfunctional variants of *CYP2C19* are three-and-a-half times more likely to experience a secondary ischemic variant than patients without the variant.[314] In other words, a large subpopulation of Plavix patients are entirely resistant to the treatment.[315] In 2011, an enormous, follow-on, meta-analysis of 42,000 patients confirmed the importance of these genetic differences,[316] and the FDA later required Sanofi to include this information on Plavix's label.[317]

But the FDA did not require, or even suggest, that Sanofi correct its underlying patents.[318] To the contrary, Sanofi's method-of-use Plavix patent makes no mention of *CYP2C19*, or even the possibility that genetic differences among patients may play a role in its effectiveness.[319] 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]," do not limit themselves to patients with functioning metabolisms of Plavix. For patients with such metabolic deficiencies, there is *no* "therapeutically effective amount" 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.[320]

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,[321] 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."[322] Under a reasonableness or

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[312] *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.").

[313] *Id.*

[314] Shah & Shah, *supra* note 308, at 702-03.

[315] *See* Hulot et al., *supra* note 312, at 2244.

[316] Michael V. Holmes et al., CYP2C19 *Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events: A Systematic Review and Meta-Analysis*, 306 JAMA 2704 (2011).

[317] *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.

[318] 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).

[319] *See* U.S. Patent No. 5,576,328.

[320] *See* 35 U.S.C. § 112(a).

[321] *See* Collins, *supra* note 7, at 1087 (describing the full-scope doctrine).

[322] Michael O'Riordan, *So Long, Plavix, What a Ride! Clopidogrel Patent Expires*, HEARTWIRE, May 17, 2012, http://www.medscape.com/viewarticle/764052.

even a single-embodiment interpretation of enablement,[323] 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,[324] when genetic sequencing was in a relative infancy.[325] 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—while future advances produce another—invalidity.[326]

Lastly, the Plavix patent demonstrates just how confusing enablement's entanglement with 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."[327] While 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

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.[328] 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.[329] Such small effects often cast doubt on whether the original clinical trials supporting cancer drugs' approval are reproducible.[330] 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 cancer.[331] The drug was later proven successful—and

[323] *See supra* notes 76-82 and accompanying text.

[324] *See* U.S. Patent No. 5,576,328.

[325] *See* ROBERT COOK-DEEGAN, THE GENE WARS 56-77 (1995) (discussing the history of genetic sequencing).

[326] *See* Lemley, *supra* note 7, at 106-07 (discussing fixing the meaning of claim terms, and consequently, enablement, at either the time the patent was filed or when it was issued).

[327] Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1359 (Fed. Cir. 1999).

[328] Ioannidis, *Research Findings*, *supra* note 3, at 697-98 (discussing small effect size and reproducibility).

[329] *See supra* notes 216-217 and accompanying text.

[330] *See* Light & Lexchin, *supra* note 3, at H2068 (discussing the incremental benefit of many approved cancer drugs).

[331] FDA, FDA BRIEFING DOCUMENT ONCOLOGY DRUG ADVISORY COMMITTEE MEETING [Avastin] 7 (July 20, 2010) [hereinafter FDA, AVASTIN], *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM219224.pdf.

approved by the FDA—to treat several other cancers, including lung, kidney, brain, and breast cancer.[332] 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.[333] Nonetheless, the FDA approved Avastin for metastatic breast cancer in 2008, although on the condition that Roche conduct two additional follow-on trials.[334]

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."[335] One clinician called the results "sobering."[336] A 2009 editorial on Avastin described its efficacy in breast cancer as "probably nonexistent, even if measured in days."[337] 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."[338] And David Gorski, a clinical oncologist and editor of the blog, *Science-Based Medicine*, called the approval results "thin gruel."[339]

Two later follow-on trials of Avastin in breast cancer proved these doubts well-founded. One trial concluded that Avastin *decreased* patient overall survival from 1.1 to 1.7 months; another found that Avastin increased overall survival but only by 2.9 months.[340] This conflicting data—and some additional evidence that Avastin was causing unwanted side effects—eventually caused the FDA to pull approval for Avastin as a treatment of metastatic breast cancer.[341]

Despite all of this, patents on Avastin as a "method of treating breast cancer" abound. For example, U.S. Patent No. 8,017,735, owned by Merck & Co., claims "[a] method for treating a [breast] cancer" by using Avastin as a combination therapy with another antibody.[342] U.S. Patent No. 8,859,542, originally assigned to Wyeth Pharmaceuticals, similarly claims "[a] method of treating [breast] cancer" by administering Avastin in conjunction with a triazine derivative.[343]

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[332] *Id.*

[333] Kathy Miller et al., *Paclitaxel Plus Bevacizumab Versus Paclitaxel Alone for Metastatic Breast Cancer*, 357 NEW ENGL. J. MED. 2666, 2670 (2007).

[334] *See* FDA, AVASTIN, *supra* note 331, at 27.

[335] Gina Kolata & Andrew Pollack, Costly Cancer Drug Offers Hope, but Also a Dilemma, N.Y. TIMES, July 6, 2008, at A1.

[336] *Id.*

[337] Fojo & Grady, *supra* note 16, at 1045.

[338] Fojo & Parkinson, *supra* note 16, at 5973.

[339] 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/.

[340] FDA, AVASTIN, *supra* note 331, at 27.

[341] FDA, *FDA News Release: 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

[342] U.S. Patent No. 8,017,735, col. 89, l. 52 (filed Nov. 19, 2004).

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

And U.S. Patent No. 9,066,963 claims "[a] method of treating breast cancer in a subject in need thereof" by using Avastin with anthracycline.[344]

Whether such inventions are indeed "cancer treatments," as they claim, likely turns on what constitutes a "treatment."[345] 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's 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,"[346] 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* where the cited references concerning a treatment for Alzheimer's was a "mere research proposal."[347] Indeed, cancer treatment patents—like cures for baldness—have been specifically spotlighted by the Federal Circuit as a "notoriously intractable area" to prove enablement.[348]

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.[349] 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 is 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.[350] To that extent, resolving questions of whether post-application evidence or new scientific advances are allowed to prove a lack of enablement becomes less important.[351] And lastly, the confusing overlap between enablement and lack of utility[352] becomes less confusing where the treatment in question appears, in some senses, useless. As with Avastin, clinicians—and the patent office—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?"[353]

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[344] U.S. Patent No. 9,066,963, col. 289, ll. 20-21 (filed Mar. 15, 2012).

[345] *Cf.* Fojo & Grady, *supra* note 16, 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.").

[346] *See supra* notes 31-34 and 39-46 and accompanying text.

[347] In re '318 Patent Infringement Litig., 583 F.3d 1317, 1324 (Fed. Cir. 2009).

[348] 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").

[349] *See supra* Part I.B (discussing these doctrines).

[350] *See supra* notes 335-339 and accompanying text.

[351] *See supra* Parts I.A, I.D.

[352] *See supra* I.C.

[353] Fojo & Grady, *supra* note 16, at 1045.

C. 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.

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 assessed the effects of easy, early patenting when combined with the pressures of FDA approval and market races.[354] By examining data concerning cancer clinical trials and firm investment, the authors concluded 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."[355] One of the drivers behind this underinvestment in early-stage treatment and prevention surrounds the "structure of the patent system":[356] that 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—drug developers have focused on treatments that maximize patent life-span.[357] This has meant, according to Budish, Roin, and Williams' 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.[358] And as for development projects that last longer than the patent term—twenty years—"essentially 100 percent are publicly funded."[359] The incentives of private cancer drug development in the U.S., 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.[360] The cost of this "corporate short-termism" is astronomical: "890,000 lost life-years . . . [valued] on the order of $89 billion."[361]

Research incentives—and their failures—aside, even the clinical trial process itself encourages irreproducible patents. Raw clinical trial data is, according to the FDA, subject to

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[354] Budish, Roin, & Williams, *supra* note 4, at 2045-46.

[355] *Id.* at 2045.

[356] *Id.*

[357] *See id.* at 2074-75.

[358] *Id.* at 2075 (Fig. 5, Panel B).

[359] *Id.* at 2074.

[360] *See id.* at 2047-49 (discussing some of the perverse incentives in allowing firms to utilize surrogate endpoints).

[361] *Id.* at 2049.

confidentiality.[362] The agency allows this for several reasons, such as ensuring patient confidentiality,[363] and allowing drug developers to protect their manufacturing processes through trade secrets.[364] But such confidentiality also limits peer assessments of clinical trials' methodology and data, making it difficult to tell whether the results seen in clinical trials are likely to be irreproducible. Where valuable patents are in play, some of which may be predicated on ultimately irreproducible data, this creates further incentives to hide the underlying data from competitors and to obfuscate results. This occurs widely in the genetic diagnostics field, where light regulation has coincided with a recent gold rush to patent basic materials and methods of the art.[365] Approval is easy, the underlying data may be kept confidential;[366] patents are valuable;[367] and robust assessments of reproducibility are scant.[368] This all "creates some unique points of conflict, with consequences for the integrity of the scientific field and for the quality of patient services."[369]

Similarly, there is little incentive to create or share clinical information after FDA approval. Patents protecting a new, approved drug are entitled to a presumption of validity, as with all other patents.[370] 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 post-application data can be used to invalidate patents in some circumstances,[371] drug developers have little incentive to engage in follow on studies in the fear of uncovering harmful data that may cast their patents—or, worse, their FDA approvals—into

[362] Eisenberg, *supra* note 19, at 380-81.

[363] Carolyne R. Hathaway et. al., *Looking Abroad: Clinical Drug Trials*, 63 FOOD & DRUG L.J. 673, 677 (2008) ("Clinical trials conducted in the United States are also subject to the Health Insurance Portability and Accountability Act (HIPAA) which, among other things, provides important privacy and security safeguards to protect the confidentiality of patients' personal health information.").

[364] W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. (forthcoming 2015) (manuscript at 35-39), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2594335 (discussing drug manufacturers protecting manufacturing processed through trade secrets).

[365] Kane, *supra* note 246, at 838.

[366] *See* Rachel Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. DAVIS L. REV. (forthcoming 2016) (manuscript at 7-11) (discussing the lack of regulation surrounding many diagnostic tests); FDA, 510(K) SUMMARY [Illumina MiSeqDx] (Nov. 18, 2013), *available at* http://www.accessdata.fda.gov/cdrh_docs/pdf12/K124006.pdf (marking approval information as confidential).

[367] *See* Jacob S. Sherkow & Christopher Scott, *Myriad Stands Alone*, 32 NATURE BIOTECH. 620, 620 (2014) (discussing the value of diagnostic patents).

[368] Lau, Ioannidis, & Schmid, *supra* note 3, at 123 (noting that "the number [of meta-analyses] is small compared with the estimate of half a million randomized controlled trials").

[369] Kane, *supra* note 246, at 838.

[370] *See* 35 U.S.C. § 282 ("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).

[371] *See supra* notes 39-55 and accompanying text.

doubt.[372] 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.

Lastly, irreproducible patents may affect competitors' development programs by discouraging research into alternative uses of known drugs. Because patents on new drugs can be obtained even with sketchy efficacy data,[373] drug developers who receive composition patents on new drugs have a de facto monopoly 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.[374] 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[375]—even if they suspect that the drug's efficacy data is likely irreproducible.

IV. ENCOURAGING REPRODUCIBILITY IN PATENT LAW

The social costs of irreproducible patents—and drug patents in particular—are high.[376] And yet, the costs of stringently requiring reproducibility for all patents may be even higher. An enablement doctrine that requires patents to be grounded only in gold standard, highly reproducible data would likely do great violence to the patent system. For drugs, it would place almost all patents behind patent law's statutory bars,[377] necessitate unduly lengthy and expensive clinical trials,[378] and infect all pharmaceutical research and development efforts with a constant sense of economic uncertainty.[379] How such a requirement would interact with the current system of generic drug approval and patent litigation would also be entirely unclear. Innovators'

[372] *See* Eisenberg, *supra* note 19, 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.")

[373] *See supra* Parts II.C and III.B.

[374] 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.").

[375] *See* Eisenberg, *supra* note 19, at 370; LAAKMANN, *supra* note 20, at 50 ("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.").

[376] *See supra* Part III.C.

[377] *See supra* notes 237-244 and accompanying text.

[378] Budish, Roin, & Williams, *supra* note 4, at 2045-46 (criticizing the use of quick, easy surrogate endpoints in clinical trials).

[379] *Cf.* Roin, *supra* note 239, at 543 ("Unfortunately, this more predictive approach to drug discovery comes at the expense of strong patent protection, because the closer an invention gets to having been produced 'according to known methods' that 'yield predictable results,' the more likely it is to be considered obvious.").

research and development budgets are sensitive enough to competitive interests.[380] Too robust of a disenablement doctrine at the expense of early patenting for uncertain technologies may have the pernicious effect of quashing more innovation than it supports.

Practical solutions to the problems of irreproducible patents, therefore, likely lie in tailoring current legal doctrines to encourage patentees to ground their patents in reliable data. Doing so would provide patentees in unpredictable technologies the appropriate levels of risk and reward when contemplating the breadth and content of their patents. It would also level the competitive playing field among patentees who, without such incentives, would simply be encouraged to file ever broader and more unsupported patents, earlier and earlier in the development cycle.[381] Using the patent laws to solve the problem of irreproducible patents—rather than focusing on the scientific enterprise or industrial incentives for research and development—also has the advantage of being easily administrable and politically palatable.[382]

There are several possible means for encouraging reproducibility in patent law. The first involves clarifying the doctrine of enablement to encourage patentees to base their applications in sound scientific data. The doctrine should explicitly allow the introduction of post-application evidence to show whether a person having ordinary skill in the patent's art could not have made or used the patented invention at the time of its filing.[383] In addition, post-application evidence should be assessed against the full-scope of the patent's claims, in line with current Federal Circuit precedent and policy against "overclaiming."[384] Consequently, the doctrine should also be detangled from its current relationship with utility and inoperability.[385] The second means for discouraging irreproducible patent data concerns easing, in some circumstances, the perverse effect of the statutory bars, which otherwise encourage patentees to ground their applications in nascent and flawed research in a race to the patent office.[386] Lastly, a third solution would require patentees to predicate their patents on publicly available data, at least where their inventions rely on empirical claims as to their inventions' function.[387] This would encourage better research design and data collection among patentees—or, at a minimum, provide

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[380] Budish, Roin, & Williams, *supra* note 4, at 2045 ("[P]rivate firms may be particularly likely to focus on the short term in the context of research and development . . . . [because] the patent system provides, perhaps inadvertently, very little incentive for private firms to engage in long- term research.").

[381] *See id.* at 2051-52 (describing the economics of this effect); Cotropia, *supra* note 16, at 93-96 (describing the negatives of early patent filing).

[382] As of this writing, six patent reform bills have been introduced in the 114th Congress. *See Patent Progress's Guide to Federal Patent Reform Legislation,* PATENT PROGRESS, (last accessed July 24, 2015), http://www.patentprogress.org/patent-progress-legislation-guides/patent-progresss-guide-patent-reform-legislation/. One law professor has noted, "The current outlook for legislative patent reform in 2015 is not so much whether reforms will be enacted but instead how far they will go." Dennis Crouch, *An Update on Patent Reform 2015*, PATENTLYO, Nov. 17, 2014, http://patentlyo.com/patent/2014/11/update-patent-reform.html.

[383] *See supra* Part I.A.

[384] *See, e.g.*, Collins, *supra* note 7, at 1085-86 (describing enablement as a function of claim scope); *see also supra* Part I.B.

[385] *See supra* Part I.C.

[386] *See* Cotropia, *supra* note 16, at 81 (describing the statutory bars encouragement of the "folly" of early patenting); Seymore, *supra* note 40, at 162 ("[T]he patent laws actually penalize inventors who fail to file early.").

[387] *See supra* notes 175-187 and accompanying text.

competitors with robust prior art to later challenge irreproducible patents. These prescriptions, taken in whole or in part, would overcome one of the primary challenges in innovation policy: aligning scientific norms with patent law.[388]

A. Clarify the Enablement Doctrine

1. Allow the Introduction of Post-Application Evidence

As highlighted by *In re '318 Patent* and *Eli Lilly*, the doctrine of enablement sets no clear rules for when post-application evidence can be introduced to challenge—or support—a patent's validity.[389] This is problematic for 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.[390] As a consequence, post-application evidence is truly essential for challenging patents grounded in irreproducible data.

Allowing post-application 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 post-application 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 post-application evidence in enablement challenges is governed judicially.[391] And there is nothing in the enablement statute to suggest that post-application evidence should never be considered in raising questions of enablement.[392] The Federal Circuit should therefore explicitly permit the introduction of post-application evidence to challenge irreproducible patents' lack of enablement—with several limits. 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

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[388] *Cf.* Eisenberg, *supra* note 26, at 1074-75 (discussing this goal in the context of the experimental use exception); Eisenberg, *supra* note 27, at 207 (same, with respect to disclosure); Arti Kaur Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW. U. L. REV. 77, 110 (1999) (same, with respect to patent acquisition).

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

[390] *See* Stodden, *supra* note 1, 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.").

[391] *See In re '318 Patent*, 583 F.3d at 1327; *Eli Lilly*, 435 F. App'x at 925-26.

[392] *See* 35 U.S.C. § 112 (2013).

invention without undue experimentation *at the time of the patent application*.[393] Accordingly, the ultimate inquiry for whether post-application evidence proves the invalidity of an issued patent should be worded as whether the post-application 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*. This standard seems in line with past precedent, the enablement statute, and the basic contours of irreproducibility in general, a scientific inquiry focused on whether an original study was, in fact, true to begin with.[394]

Second, the introduction of post-application evidence to combat enablement should not turn on whether the issue was raised by the patent examiner during prosecution, in contravention of *Eli Lilly*.[395] Patent prosecution is, in many senses, "an ongoing negotiation between the PTO and the applicant."[396] Formal challenges by the examiner to an apparent irreproducibility of a patent applications' claims therefore likely turn on the content of negotiations—or lack thereof—between an applicant and the patent office. 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.[397]

Third, post-application evidence should not be limited to only "notoriously intractable areas such as cures for baldness or cancer."[398] Other areas of scientific inquiry—and patenting—similarly suffer from irreproducible data, such as genetic testing,[399] antibody research,[400] and even social sciences.[401] 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 post-application evidence.

And fourth, the introduction of post-application evidence should be distinguished from later scientific advances that make a once-enabling patent appear disenabling.[402] Again, the traditional standard for enablement asks whether, at the time of the application, a person having ordinary skill in the art could have made or used the patented invention without undue experimentation.[403] But using scientific advances to disprove that which was previously thought to be enabled turns on a different inquiry: whether that same person having ordinary skill in the

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[393] *See* Collins, *supra* note 7, at 1098-1105 (discussing these cases); Lemley, *supra* note 7, at 106-07 (discussing this in the context of claim interpretation).

[394] *See* Ioannidis, *Research Findings*, *supra* note 3, at 696 (describing reproducibility as where "research findings are compared against the gold standard of true relationships in a scientific field").

[395] *See Eli Lilly*, 435 F. App'x at 924-25.

[396] Phillips v. AWH Corp., 415 F.3d 1303, 1317 (Fed Cir. 2005).

[397] *Cf.* The TJ 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.").

[398] *Eli Lilly*, 435 F. App'x at 924.

[399] Kane, *supra* note 246, at 838; Ioannidis et al., *Replication Validity*, *supra* note 3, at 306.

[400] Baker, *supra* note 189, at 274.

[401] Stodden, *supra* note 1, at 3-4.

[402] *Compare supra* Part I.A *with* Part I.D.

[403] Collins, *supra* note 7, at 1098-1105; Lemley, *supra* note 7, at 106-07.

art was simply mistaken about the operation of the patent. This seems too far removed from enablement's concern of satisfying patent law's quid pro quo of exclusive rights in exchange for a workable disclosure.[404] Indeed, what constitutes a workable disclosure may, itself, change over time. Inventors, who have otherwise attempted to comply with the strictures of enablement, should not be stripped of their patents on the grounds that their field has undergone a paradigm shift.[405]

2. Define the Scope of Enablement

The scope of the enablement inquiry—whether the doctrine requires that the full scope of patents' claims are enabled or only several embodiments of the claims—should also be firmly defined to discourage patentees' reliance on irreproducible data. Currently, the doctrinal flux punishes some patentees for broad claims on suspect data,[406] while it allows others to refrain from describing potentially important—and reproducible—embodiments of their inventions.[407] Crystalizing the scope of enablement may dissuade patentees from both of these ills. But it would, at a minimum, give patent applicants certainty as to how examiners and future litigants view their claims.

In line with its current trend, the Federal Circuit should fully adopt the full scope doctrine. Demanding a full scope analysis would 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.[408] It would also strongly discourage patentees from filing overbroad claims in the first instance, and 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.[409]

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.[410] Inventors, for example, may be able to fully possess and describe their *claims*—

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[404] *See supra* notes 25-27 and accompanying text.

[405] *See* KUHN, *supra* note 12, at 82-89 (discussing the jettisoning of old ideas after a paradigm shift).

[406] *See supra* notes 70-75 and accompanying text (discussing Wyeth Corp. v. Abbott Labs., 720 F.3d 1380 (Fed. Cir. 2013)).

[407] *See supra* notes 76-78 and accompanying text (discussing Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1988)).

[408] *See* 35 U.S.C. § 112(a) (2013) ("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 . . . to make and use the same . . .").

[409] *See* Holbrook, *supra* note 26, at 157-58 ("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.").

[410] *See* Chao, *supra* note 8, 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 7, at 1085 (arguing that some

even if they unaware of precise applications of their technologies.[411] 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."[412] But 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.[413] Aligning the full scope doctrine with enablement would do much to ensure that patent claims are actually enabled rather than being irreproducible.

3. Separate Enablement from Utility

Lastly, enablement should be explicitly separated from patent law's focus on utility. The overlap between the two doctrines only appears useful where *no* embodiments of the claims are workable.[414] Because of the varied nature of irreproducibility,[415] patents grounded in irreproducible data do not necessarily fail in all cases. Indeed, utility only appears to serve as a proxy for enablement where follow-on studies produce contradictory results.[416] Where future studies are simply unable to replicate prior results,[417] or produce effect sizes smaller or larger than those determined originally,[418] this does not mean that inventions based on earlier studies fail as a matter of course.

The current state of the law has the potential cause mischief if courts begin to take irreproducibility seriously. A patent with claims drawn to several irreproducible—and disenabling—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.[419] Nor would it fulfill the purpose of the utility requirement, to prohibit the patenting of trivial or useless inventions.[420] 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

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instances of after-arising technology should be covered by earlier drafted claims); Holbrook, *supra* note 26, at 158 ("To require disclosure of every variant would be extremely costly and burdensome to both the applicant and the PTO.").

[411] *See, e.g.*, Collins, *supra* note 7, at 1107-08 (discussing this in the context of protein identification and synthesis); Feldman, *supra* note 7, at 20-21 (interferons); Lemley, *supra* note 7, at 116-17 (antibodies).

[412] Chao, *supra* note 8, at 1378.

[413] *See* Seymore, *supra* note 26, at 652 ("[T]he teaching function and enablement are inextricably related . . . .").

[414] *See supra* notes 104-111 and accompanying text.

[415] *See supra* Part III.B (demonstrating the heterogeneity of irreproducibility in pharmaceuticals).

[416] *See supra* Part III.B.1 (discussing Prempro).

[417] *See* Drummond, *supra* note 1, at 2; *see also supra* Part III.B.2 (discussing Xigris).

[418] *See* Ioannidis, *Contradicted Effects*, *supra* note 3, at 222 (describing different effect sizes in follow on clinical studies); *see also supra* Part III.B.4 (discussing Avastin for use in breast cancer).

[419] *See* Seymore, *supra* note 89, at 1048 ("A low utility threshold aligns with the broad policy goals of the patent system.").

[420] *See id.* at 1075-76.

impossible or contradictory patents. Clearly differentiating the two doctrines would provide courts a single, clear avenue to assess claims of disenabling irreproducibility.

B. Easing the Statutory Bars

Perversely, the patent statute itself creates one of the strongest incentives for irreproducible patents: the statutory bars.[421] The one-year clock placed on inventors to file patent applications, running from an invention's first public disclosure or use—such as preclinical trials—encourages inventors to race to the patent office with only the most incipient data.[422] Easing the effect of the statutory bars would consequently give inventors more time to fully form the basis for, and the data underlying, their inventions.[423]

In the drug development context, this would yield several, related benefits. First, it would allow drug developers to engage in the clinical trial process without focusing on patent expiry or coverage. There would be a diminished need to race to conduct clinical trials in order to maximize patent life-span, or to design clinical trials around whether positive results will ultimately be protected by an analogous patent. Allowing an exception to the statutory bars for clinical trials would, ideally, reshift the focus of clinical trials on finding better (more saleable) treatments rather than preserving patent terms.[424] And it would also allow drug developers time to amass enough data to present stronger and more reproducible patent applications.

A second, related benefit is that an easing of the statutory bars for drug development would otherwise encourage longer-term research goals. In contrast to today's research pipelines—where no private company has conducted trials beyond the typical patent term—pharmaceutical companies could plan on clinical trials for preventing or treating early stage cancers—or, at the very least, take more seriously long term clinical end points such as overall survival.[425] Doing so would discourage reliance on unreliable markers, like various surrogate endpoints, and their inclusion in patent applications.

Third, allowing drug developers a grace period to file patent applications on new drug investigations, discourages spaghetti-method claiming: drug patents claiming multiple indications of unknown efficacy.[426] Ending the incentives surrounding this practice would simultaneously strengthen patents that deserve protection and prevent the patenting of bogus claims that deserve little.[427] It would also potentially unclutter the Orange Book—the FDA's list

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[421] *See supra* notes 238-244 and accompanying text.

[422] *See supra* notes 245-252 and accompanying text (describing this effect).

[423] *Cf.* Budish, Roin, & Williams, *supra* note 4, at 2050-52 (discussing the effects of early disclosure on research programs).

[424] *Id.* at 2051-52.

[425] *Id.* at 2070-74.

[426] *See* Sharon C. Presnell, *Advancing Technology in the Context of the Competitive Landscape: An Industrial Technologist's Perspective*, 11 WAKE FOREST J. BUS. & INTELL. PROP. L. 380, 395 (2011) ("Obtaining broad composition of matter claims on the individual novel components (cells, device) provides support for platform strategies, where the components are likely to serve multiple indications; this strategy also prevents competitors from making small changes to the final composite product and bringing forward a 'new' composition.").

[427] *See* Holbrook, *supra* note 26, at 157-58 (discussing this in the context of claims for "methods of treating cancer").

of which drugs cover which patents—that serves as a litigation clearinghouse for generic manufactures.[428]

As with clarifying enablement to resolve irreproducibility concerns, modifying the statutory bars to better suit drug development is not without potential criticisms. The statutory bars serve several critical functions in patent law, the absence of which, may interfere with innovators' disclosure incentives.[429] Nonetheless, for technologies subject to regulatory approval prior to deployment—such as drugs, biologics, and some medical devices—the purposes of the statutory bars seem outmoded. For example, the statutory bars are designed to prevent an inventor from withdrawing from the public what it previously possessed.[430] In the case of drugs regulated by the FDA, however, the public has no real possession of the invention, practically speaking, prior to the agency's approval and the drug's subsequent sale.[431] Furthermore, because drug manufacturers frequently protect the manufacture of their drugs through trade secrets, the public is often denied access to the means to effectively make drugs, even if those drugs are otherwise known.[432] The statutory bars also discourage inventors from "sleeping on their rights" and surprising competitors at a later date.[433] But this criticism cannot be applied to drug manufacturers who may wish to delay filing patent applications but otherwise engage in preclinical trials and the gauntlet of FDA filings and applications required to bring their products to market. Lastly, the statutory bars seek to prevent inventors from inequitably extending the patent term, by secretly reaping the benefits of their own technology for a period of time before seeking to disclose that technology to the patent office.[434] Yet, because drug developers cannot market their inventions prior to FDA approval, it is impossible for them to surreptitiously sell their products. In each of these cases, the goals of the statutory bars are simply not aligned with the realities of drug development.

Perhaps more practically, a number of commentators have expressed concern that exceptions to the statutory bars for drug development ultimately lengthens drugs' exclusivity terms—a bad move for generic manufacturers and antithetical, in some cases, to the purpose of the Hatch-Waxman Act.[435] It is true, relatively speaking, that patent terms would become longer under a regime with more permissive statutory bars. But longer exclusive terms, especially for complex drugs with outstanding need, are not necessarily bad. For biologics, antibiotics,

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[428] *See* Sherkow, *supra* note 318, at 214-16 (discussing the FDA's role with respect to the Orange Book).

[429] *See* Cotropia, *supra* note 16, at 81 (discussing the policy implications behind the statutory bars).

[430] Holbrook, *supra* note 26, at 153 ("[The statutory bar] provisions preclude patentability when the prior art demonstrates that the public was in possession of the invention pursuant to an enabling disclosure.").

[431] *See* Anna B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 ALA. L. REV. 305, 334 (2011) (describing arguments equating FDA approval to public access of approved medicines).

[432] Price & Rai, *supra* note 364, at 35-39.

[433] Holbrook, *supra* note 26, at 152 ("These statutory bars are exceptions to the first-to-invent system because the applicant may be precluded from obtaining a patent even if she was the first to invent the device.").

[434] *See* Cotropia, *supra* note 16, at 81 ("The statutory bar serves this function, preventing inventors from enjoying the benefits of the patented technology, via commercial development and public use, outside the twenty-year exclusivity period that starts at the filing date.").

[435] *See* Eisenberg, *supra* note 19, at 380-84 (describing one of the purposes to the Hatch-Waxman Act as early data disclosure).

pediatric drugs, and drugs with "orphan" indications, Congress has remedied the difficulties in the drug approval process by rewarding manufacturers with longer, not shorter, periods of exclusivity.[436] It is not axiomatic that, at least in the drug development context, longer exclusivity terms necessarily correlate with decreased consumer welfare.[437] In any event, the societal costs of longer patent terms may well be worth the offsetting benefits: better clinical trials with clinically meaningful endpoints, and better patents grounded in reproducible data.

C. Require Open-Access Data

One final way to encourage reproducible data in patent applications is to simply demand public access to an applicant's underlying data. To a large degree, this is already done: each applicant possesses "a duty to disclose to the [patent office] all information known to that individual to be material to patentability."[438] And that information—typically, prior art references—are recorded on each patent application's publicly available docket. But patentees nonetheless do pick and choose which information is "material to patentability." Where such information—say, raw data from a clinical trial—is not the subject of another published document, patentees may very well keep such information confidential or protect it as a trade secret. This is precisely what occurs with confidential, highly irreproducible, preclinical trial data.[439]

When considering patents predicated on such experiments, the PTO should therefore take more seriously its duty to force applicants to publicly submit such data. While such data is likely not a "printed publication,"[440] the PTO nonetheless possesses the authority to require applicants to disclose information beyond that which is publicly available. This serves the public interest by ensuring—at least, ideally—public access to the basis of the invention prior to the expiration of the patent term.[441] Such a regime would also encourage that serious applicants ensure the reproducibility of their underlying data, or restrict their claims so as not to encompass any irreproducible aspects of their research.

Requiring the disclosure of preclinical or clinical data on pharmaceutical patents also comports with the maxim that inventors should not be able to obtain both a patent and trade secret protection on the same invention.[442] Though this doctrine against double protection has some serious caveats, the principle is routinely upheld today, and even forms the basis of other,

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[436] *See generally* Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. 299, 326-53 (2015) (describing the exclusivity regimes for these, and other, classes of therapeutics).

[437] *See* Budish, Roin, & Williams, *supra* note 4, at 2061 (giving qualified support to extending exclusivity periods).

[438] 37 C.F.R. § 156 (2014).

[439] Eisenberg, *supra* note 19, at 382-83.

[440] *See, e.g.*, 35 U.S.C. § 102(a)(1) (2013) ("A person shall be entitled to a patent unless—(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention . . . .").

[441] Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences*, 49 EMORY L.J. 783, 788 (2000) (describing this in the context of DNA sequences).

[442] Dan L. Burk, *Misappropriation of Trade Secrets in Biotechnology Licensing*, 4 ALB. L.J. SCI. & TECH. 121, 130 (1994) ("For those inventions that are patentable subject matter, concurrent patent protection and trade secret protection are incompatible because the disclosure required by the patent destroys trade secrecy.").

related patent doctrines, such as obvious-type double-patenting.[443] Despite this, pharmaceutical developers engage in precisely such behavior when seeking patents on thin, but secretive, preclinical trial data.

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 post-application 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. Innovation policy must—and can—address this fundamental disconnect between science process and patent law to promote meaningful innovation. To that end, deploying changes to and clarifications of patent law appear to be attractive solutions. The doctrine of enablement can be clarified to allow the applications, and litigants, the full breadth of their arguments to prove, or disprove, enablement by way of reproducibility. The statutory bars should be relaxed to allow inventors to garner better data to support their applications on complex inventions. And, for patented therapeutics, the FDA should make their corresponding clinical trials publicly available, both as an incentive to develop better clinical trials, but also as an avenue to challenge patents grounded in spurious empirical data. These modifications would align patent law, scientific practice, and innovation policy, and prevent the current incentive structure of disenablement.

[443] Burk & Lemley, *supra* note 27, at 1687 n.418 ("[T]he doctrine of 'obviousness-type double patenting' precludes obtaining two patents that would be obvious in view of one another unless the patentee disclaims the longer patent term.").