

PATENTS, PROMISES, AND REPRODUCIBILITY

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TABLE OF CONTENTS

INTRODUCTION.....	1
I. EARLY PATENTING AND THE DOMESTIC DISCLOSURE DOCTRINES	2
A. United States: Enablement.....	3
B. The Commonwealth: The Promissory Doctrine	5
C. Europe: Industrial Application	7
II. PATENT INCENTIVES AND IRREPRODUCIBLE RESEARCH	8
III. SPECIAL PROBLEMS FOR NEW TECHNOLOGIES	11
IV. FULFILLING PATENTS' PROMISE	12
CONCLUSION.....	14

INTRODUCTION

Cutting-edge scientific research faces a global reproducibility crisis: recent advances in a variety of fields, from biopharmaceuticals, to quantum computing, to aerospace engineering, cannot be faithfully reproduced by outside researchers.¹ A recent survey of over 1,500 researchers by *Nature*—arguably the world’s premier scientific journal—found that “[m]ore than 70% of [them] have tried and failed to reproduce another scientist’s experiments.”² Scientific institutions around the world have accordingly reacted with alarm.³

Investigations into this crisis’s causes have examined almost every facet of both experimental design and the research enterprise.⁴ But the law’s contribution to irreproducibility—namely, patent law—has been overlooked. In several ways, patent law, both

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¹ See Regina Nuzzo, *Fooling Ourselves*, 526 NATURE 182, 183 (2015) (assessing newfound recognition of a reproducibility crisis).

² Monya Baker, *1,500 Scientists Lift the Lid on Reproducibility*, 533 NATURE 452 (2016).

³ See, e.g., Francis S. Collins & Lawrence A. Tabak, *NIH Plans to Enhance Reproducibility*, 505 NATURE 612, 612 (2014); *Replicability and Reproducibility Debate*, THE BRITISH PSYCHOLOGICAL SOCIETY, <http://www.bps.org.uk/what-we-do/bps/governance/boards-and-committees/research-board/research-board-resources/replicability-and-reproducibility-debate/replicability-and-reproducibility-debate> (last accessed Nov. 30, 2016) (hosting a conference at the Royal Society dedicated to measuring reproducibility in psychology); THE INTERACADEMY PARTNERSHIP, A CALL FOR ACTION TO IMPROVE THE REPRODUCIBILITY OF BIOMEDICAL RESEARCH (Sept. 2016), available at <http://tinyurl.com/IAP-Reproducibility-Statement> (convening an international group of science academies to improve the reproducibility crisis in biomedical research).

⁴ See, e.g., John P.A. Ioannidis, *Why Most Published Research Findings Are False*, 2 PLOS MEDICINE 696, 698 (2005) (listing the variety of causes of reproducibility).

domestic law and the treaties governing it, encourages researchers to disclose their inventions as quickly as possible, even on tenuous data, and even for bleeding-edge technologies with little guarantee of success.⁵ As a consequence, these patent incentives encourage only minimal disclosure of nascent and complex research precisely where more disclosure, on more robust data, would be desired.

Several domestic patent doctrines, such as enablement in the United States, the promise doctrine in much of the Commonwealth, and the industrial application requirement in Europe, would initially appear to combat such naïve disclosures.⁶ But their specific application, and international agreements with broad nondiscrimination principles, fail to adequately police irreproducible patent disclosures.⁷ Domestic institutions, therefore, often have little power to invalidate or cancel patents grounded in specious science.⁸

This lack of an appropriate retraction mechanism ultimately contributes to a cycle of irreproducible data: researchers are encouraged to file for patents earlier and earlier, on increasingly unviable data, in an effort to thwart their competition's own scientific advances.⁹ Like experimenter bias or poor scientific controls, patent law seems to play a role in fomenting irreproducible research.

I. EARLY PATENTING AND THE DOMESTIC DISCLOSURE DOCTRINES

Ideally, patents are a societal tradeoff: inventors are granted time-limited, exclusive rights to their inventions in return for full disclosures of new, significant inventions to the public.¹⁰ For simple technologies, enforcing this quid pro quo poses few problems: all domestic patent offices with examination regimes have some authority to reject patents on inventions that are not new, trivial, or fail their disclosure obligations.¹¹ But these requirements are not typically aligned with

⁵ 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).

⁶ See *infra* Part I.A-C.

⁷ *Id.*

⁸ See *infra* notes 89-91 and accompanying text.

⁹ See Cotropia, *supra* note 5, at 93-96; Jacob S. Sherkow, *Patent Law's Reproducibility Paradox*, 66 DUKE L.J. (forthcoming 2017), available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2735181 (describing this process in pharmaceutical patents).

¹⁰ See 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.”).

¹¹ See WORLD INTELLECTUAL PROPERTY ORGANIZATION, CERTAIN ASPECTS OF NATIONAL/REGIONAL PATENT LAWS (Oct. 2016), available at http://www.wipo.int/export/sites/www/scp/en/national_laws/grace_period.pdf (comparing in table format the national disclosure requirements in member countries).

the scientific processes of experimental validation, peer review, or robust statistical checks.¹² As a result, the intersection between domestic patent law and the norms of science is frequently troubled.¹³

Several domestic disclosure doctrines from much of Europe, America, and the Commonwealth would appear to combat these difficulties. At their core, they each require inventors to describe their inventions in sufficient detail to allow the public to practice the patented technology without substantial experimentation. To that end, many in the scientific community harbor the misconception that inventors must perfect their inventions before patenting or provide robust enough data to demonstrate that their inventions are thoroughly viable.¹⁴ But disclosures doctrines from around the world typically require only that an inventor have a “a definite and permanent *idea* of the complete and operative invention.”¹⁵ Working prototypes or robust, statistically powerful data are not often required.¹⁶

As a result, these domestic patent law disclosure doctrines often fail to police reproducibility in two respects: One, these doctrines encourage inventors to file for patent applications earlier and earlier—before working examples can be developed, before data and conclusions are subject to peer review, and before any broader implications of a new technology can be assessed.¹⁷ And two, the disclosure that is encouraged by these doctrines frequently operates at a level below scientific rigor—just enough to be considered legally sufficient but not enough to merit scientific reproducibility.¹⁸ Brief discussions of these doctrines, and examples of their application, follow.

A. United States: Enablement

In the United States of America, patent law contains an enablement doctrine, a requirement that patents contain a written description sufficient to “enable” others to “make and use” the claimed invention without “undue experimentation.”¹⁹ This statutory requirement arises from over a century of common law interpretation delineating the precise boundaries of sufficiency and the quantity of experimentation that, if needed to create the invention, would be impermissibly undue.²⁰ One of the more difficult interpretive areas in the United States’

¹² See Arti Kaur Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW. U. L. REV. 77, 88-94 (1999) (describing some of these scientific norms).

¹³ Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 214-16 (1987) (describing the disconnect of these norms between science and law).

¹⁴ Jacob S. Sherkow, *Protecting Products Versus Platforms*, 34 NATURE BIOTECHNOLOGY 462, 462 (2016) (noting these misconceptions).

¹⁵ *Burroughs Wellcome Co. v. Barr Laboratories, Inc.*, 40 F.3d 1223 (Fed. Cir. 1994).

¹⁶ Ted Sichelman, *Commercializing Patents*, 62 STAN. L. REV. 341, 349-351 (2010) (noting the absence of such a requirement in modern patent law—and the difficulties that arise from it).

¹⁷ See *supra* sources cited in note 12.

¹⁸ See Sherkow, *supra* note 9, manuscript at 31-40 (describing various aspects of this phenomenon for drug patents).

¹⁹ 35 U.S.C. § 112(a); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

²⁰ ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, *PATENT LAW AND POLICY: CASES AND MATERIALS* 275-276 (6th ed., 2013).

enablement requirement, however, is determining how to assess evidence of enablement—or lack thereof—arising after the filing of an inventor’s patent application.²¹ Because the statute governing enablement requires its assessment against the text of the specification, American courts have typically been reluctant to import evidence into an enablement inquiry that was created after an application has been filed.²² Nonetheless, at least some courts, including the U.S. Court of Appeals for the Federal Circuit—the exclusive appellate court for issues concerning rejected patent applications and infringement disputes—have come to understand “after arising” evidence as sometimes demonstrating whether the patent could have been successfully “made or used” at the time the application was filed.²³

This difficulty, however, poses significant problems in the field of pharmaceuticals. As is the case internationally, U.S.-based drug developers frequently patent their inventions well before they have conducted any clinical trials concerning their drugs’ use in human patients. The resulting patent claims covering such therapies nonetheless frequently contain preambles stating that the drug in question is, in fact, a “method of treatment” of a particular illness.²⁴ And in some cases, this assertion—after clinical trials and validation studies—turns out to be empirically false.²⁵ Wyeth Pharmaceutical’s patent covering hormone replacement therapy for the treatment of a menopause-associated cardiopathy was later found to *increase* the risk of heart attacks in patients.²⁶ Eli Lilly & Co.’s patent covering Xigris (drotrecogin alfa) for the treatment of sepsis was, after ten years on the market in the United States, found to simply not work.²⁷ And Sanofi’s patent covering Plavix (clopidogrel) failed to carve out a small but significant population of patients whose genetics prevented the drug from taking its full effect.²⁸ In all of these cases, after-

²¹ See Kevin Emerson Collins, *Enabling After-Arising Technology*, 34 J. CORP. L. 1083, 1098-1105 (2009) (discussing the difficulties concerning unforeseeable “after-arising” technology).

²² See, e.g., *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App’x 917, 923-24 (Fed. Cir. 2011) (rejecting evidence concerning the tenuous nature of the patent’s claims prior to robust clinical trials). Interestingly, Eli Lilly & Co.’s drug in this case, Strattera (atomoxetine), was one the same underlying pharmaceuticals giving rise to the company’s investor arbitration dispute against the Canadian government, discussed *infra* notes 40-44.

²³ *In re ’318 Patent Infringement Litig.*, 583 F.3d 1317, 1321 (Fed. Cir. 2009) (allowing after-arising evidence for the purpose of demonstrating the unfinished nature of the patent).

²⁴ *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.”); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 348 (2007) (“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.”).

²⁵ See Sherkow, *supra* note 9, manuscript at 31-39 (discussing the following examples).

²⁶ 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).

²⁷ 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>.

²⁸ Michael V. Holmes et al., *CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events: A Systematic Review and Meta-Analysis*, 306 JAMA 2704 (2011).

arising evidence demonstrated that, even at the time of the drug's patent application, treating physicians could not "make or use" the claimed invention as described.²⁹ And yet, these companies' potentially lucrative patents covering broad aspects of the underlying active ingredients and methods of using them were never invalidated for lacking enablement.³⁰

Some of this is a function of how enablement is assessed during examination in the United States. The U.S. Patent and Trademark Office does not demand robust, reproducible clinical trials before securing drug patents. Rather it requires only enough data to demonstrate a "reasonable expectation"—not scientific certainty—of an invention's success.³¹ But enablement's difficulties as a doctrine requiring the disclosure of reproducible data run deeper than that. American courts' confusion over the timing of evidence to be assessed in the doctrine;³² problems regarding the intersection between U.S. regulatory and patent law;³³ and lax utility standards in the United States,³⁴ all contribute to enablement's relative weakness as a disclosure doctrine. To parallel the U.S. Patent and Trademark Office's interpretation of enablement, the doctrines functions not assess whether others can, in fact, "make or use" a claimed invention, but whether they merely have a "reasonable expectation" of doing so.³⁵

B. The Commonwealth: The Promissory Doctrine

In several countries within the Commonwealth of Nations, patent law contains a promissory doctrine: a requirement to uphold promises of an invention's use in a patent specification.³⁶ This is a common law interpretation of the Commonwealth's comparatively stringent approach to utility.³⁷ In the words of E. Richard Gold and Michael Shortt, "The law surrounding the 'promise of the patent' holds a patent claim invalid for lack of utility if the patented invention fails to achieve a promise made in the specification, even if the invention may

²⁹ See Sherkow, *supra* note 9, manuscript at 49-50 (drawing this conclusion).

³⁰ See *id.*, manuscript at 31-39.

³¹ UNITED STATES PATENT AND TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2164.08 (11th ed. 2013) [hereinafter MPEP].

³² Collins, *supra* note 21, at 1098-1105; 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).

³³ Dmitry Karshtedt, *Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement*, 3 HAST. SCI. & TECH. L.J. 109, 137 (2011) ("Of course, standards of compliance with FDA regulations are not coextensive with the patent law's enablement requirement.").

³⁴ MERGES & DUFFY, *supra* note 20, at 255 (discussing the weakness of the utility requirement).

³⁵ Cf. MPEP, *supra* note 31, § 2164.08.

³⁶ E. Richard Gold & Michael Shortt, *The Promise of the Patent in Canada and Around the World*, 30 CANADIAN INTELL. PROP. REV. 35, 37 (2014).

³⁷ Jerome H. Reichman, *Compliance of Canada's Utility Doctrine with International Minimum Standards of Patent Protection*, 108 AM. SOC'Y INT'L L. PROC. 313, 315 (2014) (discussing the heft of the utility requirement in various jurisdictions).

otherwise possess a scintilla of usefulness.”³⁸ While the promissory doctrine is typically recognized as being peculiar to Canada, Gold and Shortt have demonstrated that the doctrine shares strong analogs to “inutility” in Australia and New Zealand.³⁹

This promissory doctrine has recently come to a head in Canada in a suit between U.S.-based pharmaceutical developer, Eli Lilly & Co., and the Canadian government.⁴⁰ There, after several appeals in Canada’s federal courts, Eli Lilly filed a Notice of Arbitration against the Canadian government under the North American Free Trade Agreement, challenging the country’s courts’ employment of the promissory doctrine to strike down two of Eli Lilly’s drug patents.⁴¹ In the underlying judicial disputes, Canadian courts had determined that Eli Lilly’s patents had either implicitly promised a long-term, clinical benefit to taking the protected drug,⁴² or that drug promised an effect in a “markedly superior fashion with a better side-effects profile” than its competitors.⁴³ In either case, the Canadian courts determined that the underlying data giving rise to those promises did not fulfill them at the time the patents were filed.⁴⁴

The Commonwealth’s promissory patent doctrine, therefore, nominally encourages disclosure by demanding patentees to prove that their inventions actually work as promised. But tethering disclosure to patents’ promises leaves room for gamesmanship.⁴⁵ Clever applicants, of course, can make exceedingly smaller promises, and disclose concomitantly less in their applications, to circumvent the promissory doctrine’s force. Further, for complex, data-driven inventions, the precise contours of the invention’s promise may not be known until much later—until far after the one-year bar against public knowledge or publication.⁴⁶ Considering Eli Lilly’s patent covering Strattera (atomoxetine), for example, Eli Lilly could not have run sufficient clinical trials within the one-year grace to conclusively demonstrate whether its product would have, indeed, had a long-term effect, as required by the Canadian court.⁴⁷ Lastly, the promissory doctrine does not aim at the heart of the problem described here: the disclosure of irreproducible results. Patentees, even within the one-year publication grace period, could experiment with their inventions for the sole purpose of providing the type of information seemingly required by the

³⁸ Gold and Shortt, *supra* note 36, at 42.

³⁹ *Id.*

⁴⁰ Eli Lilly & Co. v. Government of Canada, UNCITRAL, ICSID Case No. UNCT/14/2 (7 Nov. 2012).

⁴¹ See Notice of Arbitration, Eli Lilly & Co. v. Government of Canada, UNCITRAL, ICSID Case No. UNCT/14/2 (12 Sept. 2013) (describing the court decisions).

⁴² Novopharm Ltd. v. Eli Lilly & Co., 2010 F.C. 915, ¶ 112.

⁴³ Eli Lilly Canada Inc. v. Novopharm Ltd., 2011 F.C. 1288, ¶¶ 209-210.

⁴⁴ Gold and Shortt, *supra* note 36, at 42.

⁴⁵ Cf. Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685, 687 (2009) (defining “gamesmanship” as “private behavior that harnesses procompetitive or neutral regulations and uses them for exclusionary purposes”).

⁴⁶ See Notice of Arbitration, *supra* note 41, ¶ 39 (noting the upshot of this result).

⁴⁷ *Id.*

promissory doctrine—but not with the rigor that scientists would put faith in.⁴⁸ The promissory patent doctrine—while admirably attempting to hold patentees to their disclosures—do not necessarily encourage the sort of disclosures needed to align the Commonwealth’s patent law with its scientific traditions.

C. Europe: Industrial Application

The European Patent Convention—to date, in force in thirty-eight countries—similarly requires European patents to disclose inventions that are “susceptible of industrial application.”⁴⁹ “Of course,” as noted by Jessica C. Lai, this is a tautology: “every invention has to have an industrial application in order to be patentable.”⁵⁰ Inventions *not* susceptible to industrial application are, definitionally, not “inventions.” Further, the pertinent Implementing Regulations do little to illuminate the text, further defining “industrial application” as questioning only whether the invention “can be made or used in any kind of industry.”⁵¹

Perhaps as a consequence of these interpretive difficulties, the EPC’s industrial application requirement has long been analogized to the utility requirement in common law jurisdictions,⁵² requiring merely that a patented invention have some, virtually any, use that does not broadly violate the *ordre public*.⁵³ But the industrial application requirement is much more textured in practice, and demands patentees to explicitly disclose not only the objective of the invention but how to commercially exploit it.⁵⁴ Europe’s industrial application requirement thus, too, functions as a disclosure scheme.

This is, perhaps, best illustrated by the Boards of Appeal of the European Patent Office’s decision in *In re Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.*⁵⁵ In that case, the patent applicant originally claimed, among other things, a method of identifying chemical compounds capable of mediating biological interactions concerning a particular protein, BDP1.⁵⁶ The application clearly described BDP1 as a composition, and the protein’s general significance in several cellular functions, but failed to clearly explicate—or provide proof of—how those cellular functions provided a concrete, pharmaceutical effect, namely, the regulation of the

⁴⁸ See Sherkow, *supra* note 9, manuscript at 33-36 (discussing an analogous difficulty in enablement in the U.S. with respect to Eli Lilly’s patent covering Xigris (drotrecogin alfa)). *But see* Novopharm Ltd. v. Eli Lilly & Co., 2010 F.C. 915, ¶ 113 (commenting on the statistical controls of Eli Lilly’s clinical trials).

⁴⁹ Convention on the Grant of European Patents, art. 52(1), 29 Nov. 2000 [hereinafter European Patent Convention].

⁵⁰ Jessica C. Lai, *Myriad Genetics and the BRCA Patents in Europe: The Implications of the U.S. Supreme Court Decision*, 5 U.C. IRVINE L. REV. 1041, 1048 (2015).

⁵¹ European Patent Convention, art. 57 (29 Nov. 2000).

⁵² See, e.g., Reichman, *supra* note 37, at 317 (making this comparison).

⁵³ See MERGES & DUFFY, *supra* note 20, at 222 (discussing the *ordre public* limitation under TRIPS).

⁵⁴ See Lai, *supra* note 50, at 1043 (discussing the explicitness requirement); Huang Yan, *Living Originalism and Patent Claim Interpretation: Reconciling Past, Present and Future*, 25 FED. CIRCUIT B.J. 273, 310 (2016) (discussing the “object of the invention” requirement).

⁵⁵ *In re Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V.*, Case T 0870/04 (Bds. App. Euro. Patent Off. 2005).

⁵⁶ *Id.* ¶ 7.

growth of cancerous cells.⁵⁷ Indeed, the application was virtually silent in this regard as it was clear that the applicant had hoped to patent the compound, and its method of interaction, first, and elucidate its clinical specifics later. This was too much for both the patent examiner and the Boards of Appeal. In its decision dismissing the applicant's appeal, the Boards of Appeal tasked the applicant with laying "the whole burden . . . to the reader to guess or find a way to exploit it in industry by carrying out work in search for some practical application geared to financial gain, without any confidence that any practical application exists."⁵⁸ Even assuming, however, that the application had described BDP1's anti-cancer properties, the Boards of Appeal further noted that the data on the subject, to date, was little more than "a vague and speculative indication of possible objectives that might or might not be achievable by carrying out further research."⁵⁹

Max-Planck might therefore be read as standing for the proposition that patent applications must provide at least *some* research data demonstrating an invention's practical effect to satisfy the EPC's "industrial application" requirement. But this seemingly sensible rule does not appear to condition the quality or nature of the underlying research—the pilot research putatively required by the European Patent Office may later found to be shoddy, imprecise, or irreproducible. In this sense, the EPC's industrial application requirement—like the Commonwealth's promissory doctrine—predicates patentability on the *quantity* of data provided in an applicant's patent, not its quality. In that vein, no drugs using BDP1, to date, have been approved by either the U.S. Food and Drug Administration or the European Medicines Agency.⁶⁰

II. PATENT INCENTIVES AND IRREPRODUCIBLE RESEARCH

Domestic patent law's disclosure doctrines aside, patents operate as strong—perhaps, too strong—incentives toward irreproducible research. In competitive, fast-moving fields, like nanotechnology, researchers often "race" to their patent offices to lay claim to early iterations of developing technologies.⁶¹ Consequently, researchers have strong incentives to design experiments based on the speed, rather than the quality, of their outputs.⁶² Researchers may also be encouraged to run their experiments using fewer controls or for shorter periods of time to obtain just enough data to satisfy their domestic patent offices.⁶³ Studies imbued with such haste

⁵⁷ *Id.* ¶ 11.

⁵⁸ *Id.* ¶ 19.

⁵⁹ *Id.* ¶ 21.

⁶⁰ Recent searches of approved drugs from both agencies did not reveal any approvals where the subject active pharmaceutical ingredient consisted of BDP1, nor known analogs of BDP1. Furthermore, neither BDP1 nor peptides derived from BDP1 are listed in the controlling pharmacopeias of either jurisdiction. Lastly, to date, only four drugs have been approved with the same mechanism of action as BDP1, i.e., as a tyrosine kinase inhibitor: imatinib, gefitinib, erlotinib, and sunitinib. See Nielka P. van Erp, Hans Gelderblom, & Henk-Jan Guchelaar, *Clinical Pharmacokinetics of Tyrosine Kinase Inhibitors*, 35 *CANCER TREATMENT REV.* 692, 692 (2009). None are BDP1 proteins or variants. *Id.*

⁶¹ Mark A. Lemley, *Patenting Nanotechnology*, 58 *STAN. L. REV.* 601, 602-605 (2005).

⁶² See Cotropia, note 5, at 93-96.

⁶³ *Id.*

are prey to several drivers of irreproducible results, such as low sample sizes, a lack of statistical power, and variability in reference materials.⁶⁴

Broadly speaking, disclosure doctrines—like enablement, the promissory doctrine, or industrial application—do little to discourage such behavior.⁶⁵ To the contrary, irreproducible results may arise where a country's patent system encourages researchers to disclose their inventions, but only partially: enough to obtain patent protection but not enough to assess or replicate the results. As previously discussed, this has been well documented in the biopharmaceutical industry where the intersection of patent law, clinical trials, and trade secrets has long counseled research companies to publicize preclinical or pilot studies while failing to make public their manufacturing methods or clinical trial data.⁶⁶ The result is a woefully incomplete—and unreplicable—record of the efficacy of patented-protected drugs and medical devices.

This is not altogether surprising. Patents can serve as a substantial prize for cutting-edge technologies. Stanley Cohen and Herbert Boyer's early foundational patents covering recombinant DNA technology, for example, generated hundreds of millions of U.S. dollars in royalties,⁶⁷ well before industrial techniques—like automated “cloning” of DNA molecules—was invented.⁶⁸ Other similar foundational biotechnology patents resulted in close to \$1 billion USD in earnings in their technologies' nascency.⁶⁹ To that end the promise of patents on foundational aspects of new technologies may simply be in direct tension with patent law's disclosure requirements. Waiting to patent until the core aspects of a new technology have been fully ascertained may, simply put, be waiting too long. After all, if one waits for the robins, Spring will already be over.⁷⁰

This tension between early and late disclosure in new areas is currently at issue concerning patents covering a foundational piece of biotechnology known by the acronym CRISPR.⁷¹ CRISPR is a cheap, easy to use, and powerful gene-editing technology, heralded as the singular most important breakthrough in biotechnology in decades.⁷² But it is embroiled in a

⁶⁴ See Ioannidis, *supra* note 4, at 698 (listing these drivers of irreproducibility).

⁶⁵ See *supra* Part I.

⁶⁶ W. Nicholson Price II & Timo Minssen, Will Clinical Trial Data Disclosure Reduce Incentives to Develop New Uses of Drugs?, 33 NATURE BIOTECHNOLOGY 685, 685 (2015).

⁶⁷ Jacob S. Sherkow & Henry T. Greely, *The History of Patenting Genetic Material*, 49 ANN. REV. GENETICS 161, 170 (2015).

⁶⁸ Kary B. Mullis, *The Polymerase Chain Reaction* (Nobel Lecture) (8 Dec. 1993), http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1993/mullis-lecture.html.

⁶⁹ Alessandra Colaianni & Robert Cook-Deegan, *Columbia University's Axel Patents: Technology Transfer and Implications for the Bayh-Dole Act*, 87 MILBANK Q. 683, 690 (2009).

⁷⁰ Cf. Warren E. Buffet, *Buy American. I Am.*, N.Y. TIMES, Oct. 17, 2008 (“So, if you wait for the robins, Spring will be over.”).

⁷¹ Antonio Regalado, *Who Owns the Biggest Biotech Discovery of the Century?*, TECH. REV. (Dec. 4, 2014), <https://www.technologyreview.com/s/532796/who-owns-the-biggest-biotech-discovery-of-the-century/>. CRISPR stands for “clustered regularly interspaced palindromic repeats,” given the structure of the DNA sequences where the technology was first identified. In bacteria, it functions as a primitive immune system. *Id.*

⁷² *Id.*

patent dispute between two sets of inventors, Jennifer Doudna from the University of California, Berkeley and Emmanuelle Charpentier, then from the University of Vienna, on one hand, and Feng Zhang of the Broad Institute of MIT and Harvard, on the other.⁷³ Although Doudna and Charpentier were the first to file a more basic patent application covering CRISPR, they did not avail themselves of a particular procedure at the U.S. Patent and Trademark Office for expedited review. As a consequence, Zhang's later-filed patent application—but one with a more detailed disclosure for how to work the technology in the cells of higher organisms—was issued first. This has triggered an administrative trial at the U.S.P.T.O. and has complicated the market for licenses to the CRISPR technology.⁷⁴ While other researchers have made substantial progress in understanding the contours of CRISPR, it remains unclear whether the disclosures made in Doudna and Charpentier's initial patent application would, if used in recent advances of the technology, be reproducible.⁷⁵

Perhaps more sinisterly, the incentives that come with patent protection can be construed as a form of experimenter bias.⁷⁶ Researchers may be counseled to generate shoddy, and consequently irreproducible, results for their patent applications that they would not have otherwise attempted in more scientifically rigorous settings. This, too, seems like a logical consequence of the weaknesses in patent law's disclosure requirements and their importance to professional advancement. At their best, patents hold the promise of continued or outside funding, scientific prestige, and of course, personal lucre. These carrots are therefore a strong encouragement to report positive—and patentable—data, even faced with the sticks of potentially contradictory evidence. Like scientific publications, patents are not granted for negative results.⁷⁷

This is not to say that all early-stage patenting is bad. Early patents may allow researchers to bring their inventions to commercial fruition, as documented by one recent and thorough study of first-time patenting by startup companies.⁷⁸ And earlier patents expire earlier, sooner allowing the claimed technology into the public domain.⁷⁹ But during their lives patents also allow inventors to stymie basic research by competitors—even if the data grounding the original patent later proves invalid or incomplete. As a consequence, patents grounded in on truly

⁷³ Jacob S. Sherkow, *Law, History and Lessons in the CRISPR Patent Conflict*, 33 NATURE BIOTECHNOLOGY 256, 256 (2015).

⁷⁴ Jacob S. Sherkow, *Pursuit of Profit Poisons Collaboration*, 532 NATURE 172, 173 (2016).

⁷⁵ Sharon Begley, *Lies, Damn Lies, and CRISPR: The Legal Battle Escalates*, STAT News, Aug. 17, 2016, <https://www.statnews.com/2016/08/17/crispr-patent-battle/> (describing the dispute as centering on whether U.C. Berkeley's disclosures could have enabled a competent molecular biologist to use their technology in higher organisms).

⁷⁶ See Seymore, *supra* note 10, at 639 (“[S]ome patentees deliberately suppress crucial information or purposely craft documents that are hard to understand.”).

⁷⁷ Sean B. Seymore, *The Null Patent*, 53 WM. & MARY L. REV. 2041, 2048 (2012) (“[T]he legal system lacks a structured mechanism for capturing and disseminating negative information . . .”).

⁷⁸ J. Farre-Mensa *et al.* USPTO Economic Working Paper No. 2015-5, *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2704028.

⁷⁹ Cotropia, note 5, at 69 (“[T]he earlier a patent is filed, the earlier the patent expires, and the earlier the claimed invention becomes part of the public domain.”).

embryonic technologies seems to encourage irreproducible research—inventions that do not work the way that they claim or, worse yet, simply don't work at all.

III. SPECIAL PROBLEMS FOR NEW TECHNOLOGIES

This disconnect between scientific reproducibility and patenting poses special problems for complex or pathbreaking technologies. How much data needs to be disclosed to enable others to use inventions grounded in empirical analyses to prove their efficacy, like drugs and biologics? What are “reasonable expectations” for success of inventions in nascent fields, like quantum computing? And how can inventions predicated on molecularly complex behavior, like certain high temperature superconductors, be described *without* the use of working examples?

With respect to empirically-based inventions, like biopharmaceuticals, the PTO's own guidelines allow descriptions of single working examples, animal studies, or in vitro analyses that would not be enough to demonstrate that the inventions work in any scientifically rigorous sense.⁸⁰ In the Xigris (drotrecogin alfa) example described earlier, Eli Lilly & Co.'s patent was not grounded in any pilot or clinical studies in humans, nor even individual medical case studies. Rather, it was based on a single preclinical animal study in all of ten baboons.⁸¹ And even where later studies have affirmatively demonstrated the irreproducibility of preclinical or even clinical data, patents covering those drugs are rarely, if ever, invalidated.⁸²

In truly nascent fields, it is difficult, if not impossible, to assess the quality or quantity of data needed to ensure a “reasonable expectation” of success. Some aspects of quantum computing, for example, are notoriously unpredictable to scale.⁸³ Whereas conventional computing relies on the flow of electrons through transistors to produce binary digits, or “bits,” (i.e., the representational 1s and 0s of modern computing), quantum computers rely on atoms' quantum states to produce quantum digits, or “qubits.”⁸⁴ Physically isolating arrays of atoms to create a quantum computer remains a significant challenge.⁸⁵ And, at least to date, a large-scale quantum computer processor has yet to be created. As a consequence, the methods and data required to demonstrate the success of such a processor are unclear. Nonetheless, the U.S.P.T.O. has issued several patents covering large-scale quantum processors, implicitly reasoning that, without more concrete guidance from the field, such processors have “reasonable expectations of success.”⁸⁶

Yet other technologies traffic in machinery so large and complex—think spacecraft, particle accelerators, or even high-throughput genomic sequencers—that they must be fully built and tested *before* they can be sufficiently described, even if the basic science behind them is

⁸⁰ MPEP, *supra* note 31, § 2164.08.

⁸¹ U.S. Patent No. 6,344,197, filed Oct. 22, 1999.

⁸² Sherkow, *supra* note 9, manuscript at 33-36.

⁸³ John Preskill, *Reliable Quantum Computers*, 454 PROC. ROYAL SOC'Y (LONDON) A 385, 385 (1998).

⁸⁴ *See id.*

⁸⁵ Raj B. Patel et al., *A Quantum Fredkin Gate*, 2 SCIENCE ADVANCE e1501531 (25 Mar. 2016).

⁸⁶ *See* MPEP, *supra* note 31, § 2164.08.

sound. Knowing Bernoulli's principle, for example—the law that governs the aerodynamic lift of a curved wing—does not mean one can draw functioning schematics for an airplane. But domestic patent law's difficulties with disclosures in these areas mean that researchers can patent such complex inventions without ever demonstrating that they actually work. Famously, Blue Origin, a Washington-based aerospace company, received a 2014 patent on landing a rocket at sea—a notoriously difficult achievement—even though Elon Musk's company SpaceX, was the first to successfully demonstrate the technology two years later, in 2016.⁸⁷

Problems with patents on bleeding-edge technologies, such as these, demonstrate both the impotence—and the potential importance—of a variety of domestic disclosure doctrines. It is absurd to allowing the Patent Office to determine whether a large scale quantum computer has a “reasonable expectation of success,” in contravention of the world's scientists' best efforts. At the same time, such standards are clearly what the law allows. Domestic disclosure doctrines, in whatever their form, should therefore explicitly require that patented disclosures be sufficiently reproducible. Whether the reproducibility of new technologies is ascertained before or after filing should be of little important to the validity of the underlying patent. Making domestic disclosure doctrines more robust would consequently allow future researchers to, in fact, use patents as scientifically rigorous disclosures. Whether such a standard is better characterized as enablement, promises, or industrial applications—or some combination of these, or other requirements—is unclear. (And is, itself, probably worthy of some experimentation.)⁸⁸ What matters instead is allowing such doctrines to achieve their scientific, and not merely legal, purposes.

IV. FULFILLING PATENTS' PROMISE

Aligning the power of the patent system with the virtues of scientific enterprise will likely require a coordinated effort among several stake-holders: namely, domestic patent offices, courts, research institutions, and potentially, supranational treaty-making organizations. With respect to domestic patent offices, they have historically been poor arbiters of scientific validity.⁸⁹ Some of this is due to the limited set of tools at their disposal, namely, a narrow focus on assessing technology in light of prior publications rather than current experimental data.⁹⁰ Few patent offices rarely, if ever, ask inventors to provide confidence intervals, rerun an experiment, or provide an additional negative control. Ensuring reproducible data in patent applications, therefore, likely begins at the ground up, from examiners themselves, where technically appropriate. At the same time, it must be recognized that patent offices often have little power to

⁸⁷ J. Foust, *Patent Decision May Not Spell End of Blue Origin-SpaceX Dispute*, SPACE NEWS (10 Sept. 2015), <http://spacenews.com/patent-decision-may-not-spell-end-of-blue-origin-spacex-dispute/>.

⁸⁸ *Cf.* Lisa Larrimore Ouellette, *Patent Experimentalism*, 101 VA. L. REV. 65, 66-75 (2015) (arguing for local experimentation in structuring innovation regimes).

⁸⁹ See Jacob S. Sherkow, *And How: Mayo v. Prometheus and the Method of Invention*, 122 YALE L.J. ONLINE 351, 356-357 (noting that the U.S. Patent and Trademark Office does not have the administrative tools at its disposal to engage in scientific fact-finding).

⁹⁰ *Id.*

demand any more data from applicants than their domestic laws allow.⁹¹ Rules or directives specifying the sufficiency of disclosures cannot be changed by line examiners' whim, even in the service of their duties. But what patent offices can require, however, is for their examiners corps to take domestic disclosure doctrines more seriously. In the United States, for example, the U.S.P.T.O. could draft guidances to its examiners clarifying what constitutes a "reasonable expectation of success" for groundbreaking or empirically-driven technologies.

Courts, too, should take a harder look at how patents drive irreproducible research by reexamining their countries' disclosure requirements. While imperfect, the Commonwealth's promissory doctrine is perhaps the best singular example of the judiciary taking a more active role in aligning the legal sufficiency of disclosures with scientific reproducibility.⁹² At the same time, many U.S. courts have cabined themselves to assessing enablement solely based on information published at the time a patent was filed. But this seems to exclude later attempts to validate the patent's claims or future experiments that cast doubt on an invention's mechanism or scope of use.⁹³ That runs contrary to the purpose and importance of replication studies for newer, uncertain technologies.⁹⁴ Courts should expand their focus and recognize that patents based on irreproducible data simply do not fulfill their societal quid pro quo of disclosing working inventions in return for a patent.

Lastly—as an issue of academic integrity—research institutions must do a better job of demanding reproducible data from their investigators' patents.⁹⁵ Like scientific publications, patent applications are published all the same. Shoddy data in either venue can, and should, be an embarrassment to the institution sponsoring the underlying research. Furthermore, because universities, in countries where academic institutions can take ownership to their researchers patents, typically hire and pay their researchers' patent attorneys themselves, these institutions have the power to require more and better data on patents bearing themselves as assignees. Simply because domestic patent law may not require scientifically rigorous data does not mean that universities should follow.

Lastly, national legislatures should begin the process of rethinking the hard bars on disclosure grace periods. In the academic setting, the race to disclosure irreproducible research is complicated by these variety of doctrines concerning timing: how much time, for example, an inventor has to file for a patent once the invention has made or disclosed elsewhere, including peer-reviewed scientific publications. Generally, these "statutory bars" prohibit inventors from obtaining patents—even on their own inventions—if the inventions have been disclosed to the public for longer than a year.⁹⁶ And again, many from the scientific community appear to believe

⁹¹ See Laurence R. Helfer, *Regime Shifting: The TRIPS Agreement and New Dynamics of International Intellectual Property Lawmaking*, 29 YALE J. INT'L L. 1 (2004) (discussing the limits of line examiner input in treaty implementation some of and advantages with respect to biodiversity agreements).

⁹² See *Novopharm Ltd. v. Eli Lilly & Co.*, 2010 F.C. 915, ¶ 113 (commenting on the statistical controls of Eli Lilly's clinical trials).

⁹³ Collins, *supra* note 21, at 1104 (noting these limits).

⁹⁴ Ioannidis, *supra* note 4, at 698 (describing the importance of validation for newer technologies).

⁹⁵ Molly Silfen, *How Will California's Funding of Stem Cell Research Impact Innovation? Recommendations for an Intellectual Property Policy*, 18 HARV. J.L. & TECH. 459, 460 (2005)

⁹⁶ 35 U.S.C. § 102(a) (2015).

that they are shielded from these limits if they have submitted a manuscript for peer review confidentially, or kept their invention closely guarded among colleagues.⁹⁷ These are not poor intuitions to hold, and arguably speak volumes about the tradition and norms of disclosure in the scientific enterprise. To the extent these behaviors can be married with countries' assessment of these grace periods, legislatures should take note.

Suffice it to say that the causes of scientific irreproducibility run deep—well beyond patent law or any of the disclosure doctrines in any jurisdiction. But fixing them will indeed be but one, small advance in that regard. Doing so will go a long way toward align patents with their ideal embodiment of promoting scientific progress.

CONCLUSION

The current crisis over scientific reproducibility is mediated—in part—by global patent law. In a variety of jurisdictions, domestic patent law's disclosure requirements do little to require scientific rigor in their patent applications. The enablement doctrine in the United States, for example, often shields itself from evidence derived after a patent application has been filed, even if that information could inform a reviewing body as to what was known prior to filing. The Commonwealth's promissory doctrine, by contrast, encourages inventors to describe their inventions' objects in increasingly narrow terms, even as they strive for broader claims. And Europe's "industrial application" limitation does little to assess the quality of research underlying the claimed invention. The lack of force of these disclosure doctrines is all the more problematic for cutting-edge technologies, such as first-in-class pharmaceuticals, methods of quantum computing, and large-scale aerospace engineering projects. As a consequence, inventors are encouraged to obtain patents on their inventions on early, often less than reproducible, data. And this is exacerbated by the lucrative nature of foundational patents on groundbreaking—and uncertain—technologies. Solving these difficulties is a matter of aligning these domestic disclosure doctrines with scientific norms, and by employing various governmental stakeholders—patent offices, courts, and research institutions—to recognize this intersection between patent incentives and irreproducibility.

⁹⁷ Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 HOUS. L. REV. 1059, 1084 (2008) (summarizing research describing these and other misconceptions among academic researchers).