ARTICLES

PATENTS, PROMISES, AND REPRODUCIBILITY

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ABSTRACT

Cutting-edge scientific research faces a global reproducibility crisis: scientists often cannot faithfully reproduce their colleagues' experiments. Several domestic patent law doctrines would appear to mitigate this problem, including the enablement doctrine in the United States, the promise doctrine in Canada and the Commonwealth of Nations, and Europe's industrial application doctrine. But these doctrines' disconnect from scientific practice and their broader international harmonization make them weak tools to combat irreproducibility. Given the increase of cross-border scientific collaboration and uncertainty surrounding certain types of new technologies, these doctrines seem to exacerbate the reproducibility crisis. Making these doctrines fulfill their promises to encourage reproducible, technical disclosures will likely require effort from a variety of domestic institutions, including domestic patent offices, courts, legislatures, and universities.

I. INTRODUCTION

Cutting-edge scientific research faces a global reproducibility crisis: recent advances in a variety of fields, from biopharmaceuticals, to

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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 international and domestic, 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 patent doctrines throughout the world would initially appear to combat such naïve disclosures. In the United States, the doctrine of enablement requires patentees to sufficiently describe their inventions such that "persons having ordinary skill in the art" can make and use them.[6] In theory, patents that describe irreproducible experiments fail to describe to anyone how to make and use their underlying inventions.[7] In Canada and other parts of the Commonwealth of Nations, the promise doctrine "holds that if a patentee's patent application

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, 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 visited 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), http://tinyurl.com/IAP-Reproducibility-Statement (last visited May 11, 2018) (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 MED. 696, 697-98 (2005) (listing the variety of causes of reproducibility).

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); Jacob S. Sherkow, *Patent Law's Reproducibility Paradox*, 66 DUKE L.J. 845 (2017) (describing this process in pharmaceutical patents) [hereinafter Sherkow, *Reproducibility Paradox*].

6. 35 U.S.C. § 112(a) (2012).

7. Sherkow, *Reproducibility Paradox*, *supra* note 5, at 847.

promises a specific utility, *only if* that promise is fulfilled, can the invention have the requisite utility."[8] And in continental Europe, the industrial application requirement assesses whether patent disclosures allow the invention to be adequately "made or used in any kind of industry."[9]

Despite the potential for these three parallel doctrines, their specific application, alongside international agreements with broad harmonization principles, fail to adequately police irreproducible patent disclosures.[10] Much like international scientific standards, the weakness of these patent law doctrines has hardened across jurisdictions.[11] Domestic institutions now have little power to invalidate or cancel patents grounded in specious science. Indeed, a recent decision by the Supreme Court of Canada—*AstraZeneca Canada Inc. v. Apotex Inc.*—has all but nullified Canada's promise doctrine, in part to keep Canadian patent law harmonized with its treaty-mates.'[12]

International patent law's lack of an appropriate retraction mechanism—as there is in peer-reviewed scientific publishing—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 the commercial viability of their competitors' advances.[13] Like experimenter bias or poor scientific controls, international patent law seems to play a role in fomenting irreproducible research.

This Article in Part II first explains the problems of early patenting and patent disclosure doctrines in the United States, Canada and the Commonwealth, and Europe. Part III then shows how these requirements contribute to a cycle of irreproducible research. Part IV further explores how these difficulties particularly affect certain new technologies. Lastly, Part V briefly suggests ways to ensure international patent law's disclosure doctrines can fulfill their own promises.

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8. AstraZeneca Canada Inc. v. Apotex Inc., [2017] 1 S.C.R. 943, para. 28 (Can.).

9. Convention on the Grant of European Patents, art. 57, Nov. 29, 2000 [hereinafter European Patent Convention].

10. *Id.*

11. *See* Terttu Luukkonen, Olle Persson, & Gunnar Sivertsen, *Understanding Patterns of International Scientific Collaboration*, 17 SCI. TECH. & HUM. VALUES 101, 101 (1992) (noting that the pedigree of international scientific collaboration dates back to the nineteenth century); Daniel J. Hemel & Lisa Larrimore Ouellette, *Knowledge Goods and Nation-States*, 101 MINN. L. REV. 167, 168-70 (2016) (noting that IP treaties are designed to solve the free-riding problem).

12. *AstraZeneca*, [2017] 1 S.C.R. 943, para. 22.

13. *See* Cotropia, *supra* note 5, at 93-96; Sherkow, *Reproducibility Paradox*, *supra* note 5, at 847-48.

II. 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 them to the public, so long as they are both new and significant.[14] 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.[15] But these requirements are not typically aligned with the scientific processes of experimental validation, peer review, or robust statistical checks.[16] As a result, the intersection between domestic patent law and scientific norms is frequently troubled.[17]

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.[18] 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

14. *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").

15. *See* WORLD INTELLECTUAL PROPERTY ORGANIZATION, CERTAIN ASPECTS OF NATIONAL/REGIONAL PATENT LAWS (Aug. 2018), 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).

16. *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).

17. Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 177, 216 (1987) (describing the disconnect of these norms between science and law).

18. *See* 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) (assessing Europe's "industrial application" requirement); 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 (2014) (discussing Canada's utility requirement); Sherkow, *Reproducibility Paradox*, *supra* note 5, at 865-68 (discussing deficiencies in U.S. enablement law).

thoroughly viable.[19] But disclosure doctrines from around the world typically require only that an inventor have "a definite and permanent *idea* of the complete and operative invention."[20] Working prototypes or robust, statistically powerful data are rarely required.[21]

As a result, these domestic patent law disclosure doctrines often fail to police reproducibility in two respects. One, they 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. 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. Brief discussions of these doctrines, and examples of their application, follow.

A. *United States: Enablement*

In the United States, 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."[22] Although an invention need not be complete in every detail at the time of its patent application, "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."[23] 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.[24]

One of the interpretive difficulties with the United States' enablement requirement, however, is determining how to assess evidence of enablement—or lack thereof—arising after the filing of a patent

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

20. Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994) (emphasis added) (quoting Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986)).

21. Ted Sichelman, *Commercializing Patents*, 62 STAN. L. REV. 341, 349-51 (2010) (noting the absence of such a requirement in modern patent law—and the difficulties that arise from it).

22. 35 U.S.C. § 112(a); *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

23. Brenner v. Manson, 383 U.S. 519, 536 (1966).

24. ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 275-76 (6th ed., 2013).

application.[25] Because the statute governing enablement requires its assessment against the text of the specification, U.S. courts have typically been reluctant to import evidence into an enablement inquiry that was created after an application has been filed.[26] 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.[27]

This difficulty poses significant problems in the pharmaceutical field. 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.[28] 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.[29] In some cases, this assertion—after clinical trials and validation studies—turns out to be empirically false.[30] Wyeth Pharmaceutical's patent covering hormone replacement therapy for the treatment of a menopause-associated cardiopathy was later

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

26. *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 of the same underlying pharmaceutics giving rise to the company's investor arbitration dispute against the Canadian government. *See* Eli Lilly & Co. v. Government of Canada, UNCITRAL, ICSID Case No. UNCT/14/2, Notice of Arbitration (Sept. 12, 2013), http://icsidfiles.worldbank.org/icsid/ICSIDBLOBS/OnlineAwards/C3544/DC4612_En.pdf (noting the upshot of this result).

27. *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).

28. 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").

29. *See In re* '318 Patent, 583 F.3d at 1323.

30. *See* Sherkow, *Reproducibility Paradox*, *supra* note 5, at 876-79 (discussing the following examples).

found to *increase* the risk of heart attacks in patients.[31] 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.[32] And Sanofi's patent covering Plavix (clopidogrel) failed to account for a small but significant population of patients whose genetics prevented the drug from taking its full effect.[33] In all of these cases, after-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.[34] 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.[35]

Some of this problem is a function of how enablement is assessed during examination in the United States. The U.S. Patent and Trademark Office (USPTO) 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.[36] But enablement's difficulties as a doctrine requiring the disclosure of reproducible data run deeper than that. U.S. courts' confusion over the timing of evidence to be assessed in the doctrine,[37] problems regarding the intersection between U.S. regulatory and patent law,[38] and lax utility standards in the United

31. 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, 321 (2002).

32. Press Release, Eli Lilly & Co., Lilly Announces Withdrawal of Xigris Following Recent Clinical Trial Results (Oct. 25, 2011), https://investor.lilly.com/releasedetail.cfm?releaseid=617602.

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

34. *See* Sherkow, *Reproducibility Paradox*, *supra* note 5, at 894-95 (drawing this conclusion).

35. *See id.* at 876-85.

36. UNITED STATES PATENT AND TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2164.08 (9th ed. 2018) [hereinafter MPEP].

37. Collins, *supra* note 25, 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).

38. 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"); W. Nicholson Price, II, *Expired Patents, Trade Secrets, and Stymied Competition*, 92 NOTRE DAME L. REV. 1611, 1633-34 (2017) (noting the contest between patent

States[39] all contribute to enablement's relative weakness as a disclosure doctrine. Despite its purpose, the evidence used to support the doctrine does not assess whether others can, in fact, "make or use" a claimed invention, but whether they merely have a "reasonable expectation" of doing so.[40]

B. *The Commonwealth: The Promise Doctrine*

In Canada, and several other countries within the Commonwealth of Nations, patent law contains a promise doctrine: a requirement to uphold promises of an invention's use in a patent specification.[41] Unlike enablement in the United States—a doctrine focused more on the *description* of an invention than the claimed invention itself—the Commonwealth promise doctrine is a function of utility, an assessment of whether an invention is, in fact, *useful*.[42] In the doctrine's common law conception, for patents that contain "an explicit 'promise,' utility will be measured against that promise."[43] In addition, the "promise" of a patent arises from its construction: courts are to assess a patent's promises "within the context of a patent as a whole, through the eyes of a [person having ordinary skill in the art], in relation to the science and information available at the time of filing."[44]

The differences between the promise doctrine and enablement stem from the Commonwealth's comparatively stringent approach to utility.[45] In the United States, utility is, by far, the easiest substantive requirement for an inventor to overcome, and articles run riot with ludicrous examples of granted patents with only a comical sense of

law's disclosure requirements and those pertaining to a combination of regulatory approval and trade secrecy).

39. MERGES & DUFFY, *supra* note 24, at 255 (discussing the weakness of the utility requirement).

40. *Cf.* MPEP, *supra* note 36, § 2164.08; *see also* Jacob S. Sherkow, *Inventive Steps: The CRISPR Patent Dispute and Scientific Progress*, 18 EMBO REP. 1047, 1049-50 (2017) (comparing the U.S. and European "reasonable expectation" standard in the context of the CRISPR patent dispute) [hereinafter Sherkow, *Inventive Steps*].

41. E. Richard Gold & Michael Shortt, *The Promise of the Patent in Canada and Around the World*, 30 CANADIAN INTELL. PROP. REV. 35, 37-38 (2014).

42. *AstraZeneca*, [2017] 1 S.C.R. 943, para. 28. ("The Promise Doctrine, as developed by the Federal Courts' jurisprudence, holds that if a patentee's patent application promises a specific utility, *only if* that promise is fulfilled, can the invention have the requisite utility—'the promise of the patent is the yardstick against which utility is measured'").

43. *Id.* at para. 29.

44. *Id.* at para. 30.

45. Reichman, *supra* note 18.

usefulness.[46] But utility has long been taken more seriously outside of the United States.[47] With respect to these differences in utility between the two jurisdictions, E. Richard Gold and Michael Shortt claim that "[t]he 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 otherwise possess a scintilla of usefulness."[48] And while the promise doctrine is typically recognized as being "uniquely Canadian,"[49] a number of commentators have demonstrated that the doctrine shares strong analogs to "inutility" in Australia and New Zealand[50] and the "False Promise doctrine" in the courts of the United Kingdom.[51]

Beginning in the mid-2000s, the promise doctrine shone as a beacon of hope against irreproducibility, especially in pharmaceutical patents. A number of federal court cases in Canada reaffirmed the vitality of the promise doctrine in Canada to invalidate patents that promised much but demonstrated little.[52] In 2005, in *Bristol-Myers Squibb Co. v. Apotex Inc.*, the Federal Court of Canada, concluded that Bristol-Myers Squibb's patent covering nefazodone for treating depression actually "promise[d] 'improved antidepressants with minimal side effect potential'" and put the issue to trial after discovery.[53] Similarly, in 2009, two cases employed the promise doctrine to cast doubt on patents covering angiotensin-converting enzyme (ACE) for cardiac disease. In *Laboratoires Servier v. Apotex Inc.*, the Canadian Federal Court of Appeal affirmed the invalidation of ADIR's patent covering a group of ACE inhibiting compounds on the grounds that, despite the patent's promise, not all of the compounds in fact inhibited ACE.[54] And in *Sanofi-Aventis Canada Inc. v. Apotex Inc.*, the Federal Court of Canada similarly ruled that Sanofi-Aventis's Altace (ramipril) similarly failed to make good on its patent's promise to both inhibit

46. *See, e.g.*, Michael Risch, *A Surprisingly Useful Requirement*, 19 GEO. MASON L. REV. 57 (2011) ("In the broad scheme of things, however, the requirement that an invention be useful has been nearly nonexistent—essentially ignored. . . . Patent applications that fail to meet this standard are rare, usually claiming perpetual-motion machines, chemicals with unknown effects, and other fantastic concepts").

47. *See* Reichman, *supra* note 18.

48. Gold & Shortt, *supra* note 41, at 42.

49. *AstraZeneca*, [2017] 1 S.C.R. 943, para. 33 (citing cases).

50. Gold & Shortt, *supra* note 41, at 53.

51. *AstraZeneca*, [2017] 1 S.C.R. 943, para. 33-35 (citing Norman Siebrasse, *The False Doctrine of False Promise*, 29 CAN. INTELL. PROP. REV. 3 (2013)).

52. *Id.* at para. 32 (citing cases).

53. 2005 F.C. 1348, para. 16 (Can. Fed. Ct.).

54. 2009 F.C.A. 222, para. 100-13 (Can. C.A.).

ACE and mitigate hypertension.[55] Finally, in 2012, in *AstraZeneca Canada Inc. v. Mylan Pharmaceuticals ULC*, the Canadian Federal Court of Appeal concluded that while "an invention that does not do what the specification promises lacks utility," AstraZeneca's cancer drug patent made no such promises.[56]

Recently, however, the Supreme Court of Canada has done away with much of the promise doctrine. In *AstraZeneca Canada Inc. v. Apotex Inc.*, AstraZeneca's patent covering Nexium (esomeprazole) touted improved metabolic properties (over a chiral variant of the same drug) such that the stomach-acid reducing drug would work for a wider variety of people than previous formulations.[57] At trial, however, the judge concluded that this promise was not met at the time the patent was filed because these improved properties of the drug were "neither demonstrated nor soundly predicted at the filing date."[58] The Canadian Federal Court of Appeal agreed, and, in doing so, "affirmed both the status and application of the Promise Doctrine."[59] The Supreme Court, however, disagreed. It allowed the appeal primarily on the grounds that the promise doctrine—as a whole—was an "unsound . . . interpretation of the utility requirement that is incongruent with both the words and the scheme of the *Patent Act*."[60] The promise doctrine, in the eyes of the Court, sewed confusion as to what constituted *promises* rather than mere *hopes* of utility described in a patent's specification—something the Court previously sought to clarify in its 1981 decision, *Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd.*[61] Further, and in a mortal blow to the doctrine's protection against irreproducibility, the *AstraZeneca* Court faulted the promise doctrine for requiring patentees to vouch for *all* promises made in a patent.[62] To the

55. 2009 F.C. 676, para. 119-28 (Can. Fed. Ct.).

56. 2012 F.C.A. 109, para. 7 (Can. C.A.).

57. *AstraZeneca*, [2017] 1 S.C.R. 943, para. 9.

58. *Id.*

59. *Id.* para. 12

60. *Id.* para. 36.

61. Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd., [1981] 1 S.C.R. 504 (Can.). *Consolboard* concerned a patent covering wafer-formed wood particle board that the Federal Court concluded was invalid because it promised but did not explicitly teach making the boards by cross-cutting. The Supreme Court of Canada allowed the appeal because a person having ordinary skill in the woodworking art would have known how to cross-cut the boards despite the lack of an explicit teaching. The Federal Court opinion, the *Consolboard* Court concluded, "confused the requirement of s. 2 of the Patent Act defining an invention as new and 'useful,' with the requirement of s. 36(1) of the Patent Act that the specification disclose the 'use' to which the inventor conceived the invention could be put. The first is a condition precedent to an invention, and the second is a disclosure requirement, independent of the first." *Id.* at 527.

62. *AstraZeneca*, [2017] 1 S.C.R. 943, para. 47.

contrary, the Court concluded that utility was unitary: that because "every invention pertains to a *single* subject-matter . . . *any* single use of that subject-matter that is demonstrated or soundly predicted by the filing date is sufficient to make an invention useful."[63]

Despite its subjectivity, this reading of the promise doctrine is problematic. At its best, the promise doctrine nominally encourages disclosure by demanding patentees to prove that their inventions actually work as promised. Allowing patentees, by contrast, to describe their invention as working in a broad series of applications—but mandating that they only demonstrate "*any* single use"—is not so much holding patentees to their societal bargains as it is countenancing the spaghetti method.[64]

But even at its best, the promise doctrine was never perfect. Tethering disclosure to patents' promises leaves room for gamesmanship.[65] Clever applicants, of course, can make exceedingly smaller promises, and disclose concomitantly less in their applications, to circumvent the promise 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.[66] Consider Eli Lilly's patent covering Strattera (atomoxetine), for example. 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 promise doctrine to strike down two of Eli Lilly's drug patents.[67] 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,[68] or that the drug promised an effect in a "markedly superior fashion with a better side-effects profile" than its competitors.[69] 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

63. *Id.* para. 49.

64. *Cf.* NEIL SIMON, THE ODD COUPLE 75-76 (1966) (throwing an entire plate of spaghetti—or was it linguine?—against a kitchen wall).

65. *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").

66. *See* Eli Lilly & Co., *supra* note 26, ¶ 39 (noting the upshot of this result).

67. *See id.*

68. Novopharm Ltd. v. Eli Lilly & Co., 2010 F.C. 915, para. 112 (Can.).

69. Eli Lilly Canada Inc. v. Novopharm Ltd., 2011 F.C. 1288, para. 209-10 (Can.).

filed.[70] But a true assessment of either of these promises—a long term clinical benefit or comparatively diminished side-effects—would have taken much more than a year from when Eli Lilly first began trials in humans.[71] As a consequence, Eli Lilly could not have proven its patents' promises within the one-year grace period to as required by the Canadian court.[72] Taking the promise doctrine seriously, here, merely counsels making fewer—and poorer—promises.

Lastly, the promise 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 promise doctrine but not with the rigor that scientists would put faith in.[73] The promise patent doctrine, dead or alive, does 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, in force in thirty-eight countries to date, similarly requires European patents to disclose inventions that are "susceptible of industrial application."[74] "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."[75] Inventions *not* susceptible to industrial application are, by definition, 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."[76]

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,[77] requiring merely that a patented invention have some, virtually any, use that does not broadly

70. Gold & Shortt, *supra* note 41, at 42.

71. *Id.*

72. *Id.*

73. *See* Sherkow, *Reproducibility Paradox*, *supra* note 5, at 889-92 (discussing an analogous difficulty in enablement in the U.S. with respect to Eli Lilly's patent covering Xigris (drotrecogin alfa)). *But see Novopharm*, 2010 F.C. 915, para. 113 (commenting on the statistical controls of Eli Lilly's clinical trials).

74. European Patent Convention, *supra* note 9, art. 52(1).

75. Lai, *supra* note 18, at 1048.

76. European Patent Convention, *supra* note 9, art. 57.

77. *See, e.g.*, Reichman, *supra* note 18, at 317 (making this comparison).

violate the *ordre public*.[78] 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.[79] 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 Fo«rderung der Wissenschaften e.V.*[80] 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.[81] 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 growth of cancerous cells.[82] 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.[83] 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."[84] 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."[85]

Max-Planck might therefore be read as standing for the proposition that patent applications must provide at least *some* research data

78. *See* MERGES & DUFFY, *supra* note 24, at 222 (discussing the *ordre public* limitation under TRIPS).

79. *See* Lai, *supra* note 18, 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).

80. Case T 0870/04 (European Patent Office, Tech. Bd. App.).

81. *Id.* para. 7.

82. *Id.* para. 11.

83. *Id.*

84. *Id.* para. 19.

85. *Id.* para. 21.

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 promise 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.[86]

III. 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.[87] Consequently, researchers have strong incentives to design experiments based on the speed, rather than the quality, of their outputs.[88] 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.[89] Studies imbued with such haste are prey to several drivers of irreproducible results, such as low sample sizes, a lack of statistical power, and variability in reference materials.[90]

Broadly speaking, disclosure doctrines—like enablement, the promise doctrine, or industrial application—do little to discourage such behavior.[91] 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

86. 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. None are BDP1 proteins or variants. *See* Nielka P. van Erp, Hans Gelderblom, & Henk-Jan Guchelaar, *Clinical Pharmacokinetics of Tyrosine Kinase Inhibitors*, 35 Cancer Treatment Rev. 692, 692 (2009).

87. Mark A. Lemley, *Patenting Nanotechnology*, 58 Stan. L. Rev. 601, 602-05 (2005).

88. *See* Cotropia, *supra* note 5, at 93-96.

89. *Id.*

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

91. *See supra* Part I.

enough 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.[92] The result is a woefully incomplete and non-replicable record of the efficacy of patent-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,[93] well before industrial techniques like automated "cloning" of DNA molecules were invented.[94] Other similar, foundational biotechnology patents resulted in close to $1 billion USD in earnings in their technologies' nascence.[95] 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.[96]

This tension between early and late disclosure in new areas is currently at issue for patents covering a foundational piece of biotechnology known by the acronym CRISPR.[97] CRISPR is a cheap, easy-to-use, and powerful gene-editing technology, heralded as the single most

92. 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); W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 526 (2014).

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

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

95. 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).

96. *Cf.* Warren E. Buffet, *Buy American. I Am.*, N.Y. TIMES, Oct. 17, 2008, at A33 ("So, if you wait for the robins, Spring will be over.").

97. Antonio Regalado, *Who Owns the Biggest Biotech Discovery of the Century?*, MIT 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.*

important breakthrough in biotechnology in decades.[98] But it is embroiled in a patent dispute between two sets of inventors: on the one hand, Jennifer Doudna from the University of California, Berkeley and Emmanuelle Charpentier, then from the University of Vienna; and, on the other, Feng Zhang of the Broad Institute of MIT and Harvard.[99] Although Doudna and Charpentier were the first to file a more basic patent application covering CRISPR, they did not avail themselves of expedited review at the USPTO.[100] As a consequence, Zhang's later-filed patent application, one with a more detailed disclosure for how to work the technology in the cells of higher organisms, was issued first.[101] This triggered an administrative trial at the USPTO,[102] and has complicated the market for licenses to the CRISPR technology.[103] 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, have been reproducible.[104]

Perhaps worse, the incentives that come with patent protection can be construed as a form of experimenter bias.[105] 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.[106] This, too, seems like a logical consequence of the weaknesses in patent law's disclosure

98. *Id.*

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

100. Broad Institute, Inc. v. Regents of the Univ. of Cal., No. 106,048, 2017 WL 657415 (P.T.A.B. Feb. 15, 2017).

101. *Id.*

102. *Id.*

103. Jorge L. Contreras & Jacob S. Sherkow, *CRISPR, Surrogate Licensing, and Scientific Discovery*, 355 SCIENCE 698, 698-70 (2017); Jacob S. Sherkow, *Pursuit of Profit Poisons Collaboration*, 532 NATURE 172, 173 (2016).

104. 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).

105. *See* Seymore, *supra* note 14, at 639 ("[S]ome patentees deliberately suppress crucial information or purposely craft documents that are hard to understand").

106. *See* Cotropia, *supra* note 5, at 76 ("If patent law required a use of a certain commercial or social worth, an inventor would need to take time to establish that her invention provides this level of benefit before filing. She would need to find a commercially beneficial use for her invention. Then she would need to produce the data necessary to prove that her invention actually generated such a benefit. . . . This additional proof is just not required under the current utility standard for patentability").

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.[107]

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.[108] And earlier patents expire earlier, sooner allowing the claimed technology into the public domain.[109] 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 truly embryonic technologies seem to encourage irreproducible research—inventions that do not work the way that they claim or, worse yet, simply do not work at all.

IV. 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 USPTO'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.[110] In the Xigris example described earlier,[111] Eli Lilly & Co.'s

107. 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 . . . .").

108. Joan Farre-Mensa et al, *What is a Patent Worth? Evidence from the U.S. Patent "Lottery"* (USPTO Economic Working Paper No. 2015-5), http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2704028.

109. Cotropia, *supra* 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"); John F. Duffy, *Rethinking the Prospect Theory of Patents*, 71 U. Chi. L. Rev. 439, 440 (2004).

110. MPEP, *supra* note 36, § 2164.08.

111. *See* Press Release, *supra* note 32, and accompanying text.

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.[112] Even where later studies have affirmatively demonstrated the irreproducibility of preclinical or even clinical data, patents covering those drugs are rarely, if ever, invalidated.[113]

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. This is, in fact, the heart of the dispute in the CRISPR case: whether Doudna and Charpentier's landmark 2012 paper describing an engineerable form of the technology *in vitro* provided average molecular biologists a "reasonable expectation of success" of translating it to human cells.[114] The U.S. Patent Trial and Appeal Board (PTAB) found that numerous complexities in the cells of higher organisms, eukaryotes, gave scientists pause as to whether Doudna and Charpentier's invention would work there.[115] The PTAB recited a substantial body of evidence from the parties' experts, including statements made by Doudna, and explaining doubts about using the technology in eukaryotes.[116] At the same time, experiments conducted almost immediately after Doudna and Charpentier's patent application was filed showed that these difficulties could be overcome with relatively conventional techniques.[117] Predicting which experiments can be used to demonstrate the applicability of routine techniques to new genetic engineering technologies remains a billion-dollar question.[118]

In other fields, such as quantum computing, experiments are notoriously unpredictable to scale.[119] Whereas conventional computing relies on the flow of electrons through transistors to produce binary digits, or

112. U.S. Patent No. 6,344,197 B2 (filed Oct. 22, 1999).

113. Sherkow, *Reproducibility Paradox*, *supra* note 5, at 886.

114. *See Broad Institute*, 2017 WL 657415, at *2.

115. *Id.* at *16.

116. *Id.* at *8-12.

117. *Id.* at *12-14.

118. *Compare id.* at *12-14 (describing the use of routine techniques in molecular biology as demonstrating the applicability of CRISPR), *with* Ben Fidler, *Reality Check: Cancer Experts Discuss Hurdles Facing CAR-T Therapy*, XCONOMY (Sept. 18, 2015), http://www.xconomy.com/national/2015/09/18/reality-check-cancer-experts-discuss-hurdles-facing-car-t-therapy/ (discussing difficulties facing developers of CAR-T, a genetic engineering technology, in using routine techniques of molecular biology), *and* Damian Garde & Meghana Keshavan, *Juno Halts Its Immunotherapy Trial for Cancer After Three Patient Deaths*, STAT NEWS, July 7, 2016, https://www.statnews.com/2016/07/07/juno-cancer-immunotherapy-deaths/ (discussing the surprising deaths of research subjects when subjected to a combination of an experimental therapy and routine chemotherapy agent).

119. John Preskill, *Reliable Quantum Computers*, 454 ROYAL SOC'Y 385, 385 (1998).

"bits," (i.e., the representational 1s and 0s of modern computing), quantum computers rely on atoms' quantum states to produce quantum digits, or "qubits."[120] Physically isolating arrays of atoms to create a quantum computer remains a significant challenge.[121] 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 USPTO 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."[122]

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 sound. Knowing, for example, Bernoulli's principle—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.[123]

Problems with patents on bleeding-edge technologies, such as these, demonstrate both the impotence—and the potential importance—of a variety of disclosure doctrines in patent law. It is absurd to allow any jurisdiction's patent office to declare that a quantum computer has a "reasonable expectation of success," despite the efforts of the world's best scientists. At the same time, such standards are clearly what the law allows in the United States, Europe, and the Commonwealth.[124] Domestic disclosure doctrines, in whatever their form, should therefore explicitly require that patented disclosures be sufficiently reproducible.[125] Whether the reproducibility of new technologies is ascertained before or after filing should be of little importance to the validity of the

120. *See id.*

121. Raj B. Patel et al., *A Quantum Fredkin Gate*, 2 SCI. ADVANCE e1501531 (2016).

122. *See* MPEP, *supra* note 6, § 2164.08.

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

124. *See supra* Part I.

125. *See* Sherkow, *Reproducibility Paradox*, *supra* note 5, at 903 (making this recommendation with respect to enablement in the United States).

underlying patent. Making domestic disclosure doctrines more robust would consequently allow future researchers to 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.[126] What matters instead is allowing such doctrines to achieve their scientific, and not merely legal, purposes.[127]

V. Fulfilling Patents' Promise

Aligning the power of the patent system with the virtues of scientific enterprise will likely require a coordinated effort among several stakeholders: 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.[128] 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.[129] Few patent offices rarely, if ever, ask inventors to provide confidence intervals, rerun an experiment, or provide an additional negative control.[130] 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 demand any more data from applicants than their domestic laws allow.[131] Rules or directives specifying the sufficiency of disclosures cannot be changed by line examiners' whims, even in the service of their duties.

What patent offices can require, however, is for their examiners corps to take domestic disclosure doctrines more seriously. In the

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

127. *See* Sherkow, *Inventive Steps*, *supra* note 40, at 1045-46 (discussing the disconnect between these standards in law and science).

128. *See* Jacob S. Sherkow, *And How:* Mayo v. Prometheus *and the Method of Invention*, 122 Yale L.J. Online 351, 356-57 (noting that the U.S. Patent and Trademark Office does not have the administrative tools at its disposal to engage in scientific fact-finding).

129. *Id.*

130. *See id.* (discussing these deficiencies with the USPTO).

131. *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).

United States, for example, the USPTO could draft "Guidances,"—non-binding, but strongly persuasive memoranda—to its examiners clarifying what constitutes a "reasonable expectation of success" for groundbreaking or empirically driven technologies. In fact, this is the procedural vehicle the USPTO typically deploys to instruct its examiner corps after ground-breaking decisions from the U.S. Supreme Court or the U.S. Court of Appeals for the Federal Circuit, or major scientific breakthroughs.[132] The EPO similarly issues Guidelines for Examination.[133] The Canadian Intellectual Property Office, meanwhile, infrequently puts out "Practice Notices," both to practitioners and its examining corps.[134] These Guidances can act very well as "policy levers":

> legal principles that can be applied with sensitivity to the industry and the factual context" of certain inventions.[135] A guidance gives a domestic patent offices a hand in "'making' law because it adds new content to the previous, unclarified law. . . . in response to new statutes, new judicial opinions, and new facts such as the emergence of new technology.[136]

The rise of irreproducible research cited in patents is precisely the type of technological development that calls for such a policy lever, rather than a wholesale rewriting of statutory law. Nonetheless, courts should also take a harder look at how patents drive irreproducible research by reexamining their countries' disclosure requirements. While imperfect, the Commonwealth's now recently deceased promise doctrine was perhaps the best singular example of the judiciary taking a more active role in aligning the legal sufficiency of disclosures with scientific reproducibility.[137] At the same time, many U.S. courts have cabined themselves to assessing enablement solely based on information

132. Wen Xue, Note, *Obviousness Guidance at the PTO*, 5 N.Y.U. J. INTELL. PROP. & ENT. L. 306, 326-33 (2016) (describing the Guidance process).

133. EUROPEAN PATENT OFFICE, GUIDELINES FOR EXAMINATION IN THE EUROPEAN PATENT OFFICE (Nov. 2016), http://documents.epo.org/projects/babylon/eponet.nsf/0/0791474853510FFFC125805A004C9571/$File/guidelines_for_examination_en.pdf.

134. *See* Patent Notices – Canadian Intellectual Property Office, GOVERNMENT OF CANADA, https://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/h_wr00292.html.

135. Mark A. Lemley & Dan L. Burk, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1670 (2003).

136. *See* Xue, *supra* note 132, at 329.

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

published at the time a patent was filed.[138] 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.[139] That runs contrary to the purpose and importance of replication studies for newer, uncertain technologies.[140] 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.

Additionally, as an issue of academic integrity, research institutions must do a better job of demanding reproducible data from their investigators' patents.[141] Like scientific publications, patent applications are published.[142] Shoddy data in either venue can, and should, be an embarrassment to the institution sponsoring the underlying research. Furthermore, because in countries where academic institutions can take ownership of their researchers' patents, universities 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.[143] 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 disclose 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.[144] Generally, these "statutory bars" prohibit inventors from obtaining patents—even

138. *See* Sherkow, *Reproducibility Paradox*, *supra* note 5, at 907-11.

139. Collins, *supra* note 25, at 1104 (noting these limits).

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

141. 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).

142. 35 U.S.C. § 122(b) (2012) (setting for patents' and patent applications' publication requirements).

143. *See* Brian J. Love, *Do University Patents Pay Off? Evidence from a Survey of University Inventors in Computer Science and Electrical Engineering*, 16 YALE J.L. & TECH. 285, 304-05 (2014) (describing survey data calculating the rate at which universities pay patents' prosecution fees).

144. *See* 35 U.S.C. §§ 102(a) and 102(b)(1)(A) (2016) (allowing a one-year grace period for inventions previously disclosed by the inventor in scientific applications); European Patent Convention, *supra* note 9, art. 55(1)(b) (allowing a six-month grace period for inventions previously disclosed at an "official . . . international exhibition"). *See also* Mark Schafer, Note, *How the Leahy-Smith America Invents Act Sought to Harmonize United States Patent Priority with the World*,

on their own inventions—if the inventions have been disclosed to the public for longer than a year.[145] The rule is even more stringent in Europe, which has practically no grace period.[146] Again, many from the scientific community appear to believe 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.[147] These should not be 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 aligning patents with their ideal embodiment of promoting scientific progress.[148]

VI. Conclusion

The current crisis over scientific reproducibility is caused 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 promise doctrine, by contrast, previously encouraged 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

A Comparison with the European Patent Convention, 12 Wash. U. Global Stud. L. Rev. 807, 824-26 (2013) (comparing these two provisions).

145. *See, e.g.*, 35 U.S.C. §§ 102(a) and 102(b)(1) (2016).

146. *See* Schafer, *supra* note 144, at 826 (describing the exception as "narrower").

147. 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).

148. *Cf.* Rai, *supra* note 16, at 88-94 (discussing this ideal).

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.