INCREMENTAL IMPROVEMENT OF THE PATENTABILITY STANDARD OF NONOBVIOUSNESS

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Patents incentivize innovation, but the face of innovation has changed over the past several decades. Patent law is adapting to the radical growth of the pharmaceutical and biotechnological industries, which produce drugs and biologics respectively. Research and development ("R&D") in these fields is largely incremental—new products are often derived from existing products. However, patents do not protect "obvious" improvements, those that anyone skilled in the relevant scientific field could have discovered through predictable, routine work. The line between incremental R&D and routine, obvious improvements is difficult to draw. The U.S. Court of Appeals for the Federal Circuit and the Patent Trial and Appeal Board have become critical of incremental R&D, in turn discouraging what they find to be "routine optimization." This Note describes the modern obviousness standard as it applies to the improvement of drugs and biologics and examines arguments for and against protecting incremental innovation. In light of these considerations, this Note argues that modern expectations for innovation should be updated and advocates for a stricter, narrower definition of obviousness that reflects the value of incremental R&D to the continued growth of the pharmaceutical and biotechnological industries.

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INTRODUCTION

Obvious inventions of drugs and biologics are unpatentable.[1] An obvious invention is one that someone else within the patentee's field would have been able to develop from the information available at the time of invention without spending excessive time experimenting with other options.[2] In the pharmaceutical and biotechnological sciences, researchers often improve existing drugs and biologics, respectively, to derive new inventions, known as derivative products.[3] They do so by modifying known variables, such as pH and temperature, to alter products or discover new medical uses for unmodified products through incremental research and development ("R&D").[4] Patents protecting derivative drugs and biologics are more vulnerable to invalidation on obviousness grounds than those for entirely new products.[5] When these patents are challenged, courts and the U.S. Patent and Trademark Office (USPTO) examine whether the patentee routinely optimized variables that were already predicted within the field to confer the observed benefits.[6] An effective obviousness inquiry therefore requires an understanding of what is "routine" within the pharmaceutical and biotechnological sciences.[7]

Outcomes to obviousness challenges are uncertain because the modern standard for obviousness is malleable.[8] Drugs and biologics are adjudicated using a standard originally designed for more predictable sciences, such as mechanical engineering.[9] Patent challengers can exploit the presence of "result-effective variables," variables recognized by prior researchers as potential avenues for improvement.[10] For example, if you want to keep your food from getting stale, you might put it in an airtight container. Because air exposure is a variable that affects food freshness, reducing exposure is an obvious step for improvement.[11] In the mechanical arts, variables similarly have predictable results, so their optimization requires less "guidance or

1. 35 U.S.C. § 103.
2. *See* MPEP § 2142 (9th ed. Rev. 7, Feb. 2023).
3. *See generally* STEVEN GLOBERMAN & KRISTINA M. LYBECKER, FRASER INST., THE BENEFITS OF INCREMENTAL INNOVATION: FOCUS ON THE PHARMACEUTICAL INDUSTRY (2014).
4. *See* Israel Agranat & Hili Marom, *In Defense of Secondary Pharmaceutical Patents in Drug Discovery and Development*, 11 AM. CHEM. SOC'Y MED. CHEMISTRY LETTERS 91, 91 (2020).
5. *See id.*
6. MPEP § 2144.05.
7. *Id.*
8. *See* KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 415 (2007) ("Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach . . . .").
9. *See generally* Rachel Teitelbaum & Mark Cohen, *Obviousness, Hindsight and Perspective: The Impact of* KSR v. Teleflex *on Biotech and Pharmaceutical Patents*, 25 NATURE BIOTECHNOLOGY 1105 (2007). Although *KSR* examined an invention of automotive engineering, the holding introduced uncertainty to application of the nonobviousness standard to the pharmaceutical and biotechnological arts. *Id.*
10. Moshe K. Wilensky, *The Rise of the Result-Effective Variable*, 2 LANDSLIDE 42, 42 (2009).
11. *See generally* Simon Angelo Cichello, *Oxygen Absorbers in Food Preservation: A Review*, 52 J. FOOD SCI. TECH. 1889 (2015).

direction."[12] However, variables known to affect the success of drugs and biologics are harder for researchers to control—merely making a treatment more predictable and reliable can be challenging.[13] The current standard for obviousness discounts the challenges that companies face in seeking to improve product safety and efficacy.[14]

Because the obviousness inquiry is subjective and flexible, it is subject to fluctuating trends in patent perspectives. Patent law reconciles opposing interests in promoting both disruptive innovation and accessible healthcare.[15] Companies only invest in R&D of patentable products, but consumers have an inelastic demand for drugs and biologics to achieve physical and mental well-being.[16] Patent protection is necessary for scientific progress, but high prices mean that everyone does not benefit equally from that progress.[17] Over the past few decades, patent reform has oscillated from protecting companies to protecting consumers, but a balance has yet to be reached by lawmakers and regulators.[18] Current proposals targeting incremental improvements of drugs and biologics may increase the uncertainty of patent validity and prove costly for pharmaceutical and biotechnology companies.[19]

This Note argues that the USPTO should adopt a definition of obviousness that (1) recognizes the unpredictability of drug and biologic development and (2) is less subjective and vulnerable to fluctuating trends. Part I characterizes the current obviousness standard and the areas that remain subject to unpredictable interpretation by both the U.S. Court of Appeals for the Federal Circuit and USPTO, including the treatment of result-effective variables. Part II examines the tension underlying the question of whether patent law should protect pharmaceutical and biotechnological companies' investments in incremental innovation. Finally, Part III argues that modern applications of the flexible obviousness standard are damaging to incremental R&D. This Note concludes by arguing that a more rigid standard for obviousness can reduce industry reliance on overbroad patent portfolios and promote continued improvements in the safety and efficacy of drugs and biologics.

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12. MPEP § 2164.03 (quoting *In re* Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970)).

13. *See* Holger Tostmann, *Protecting Chemistry Inventions: The Double-Edged Sword of Being an Unpredictable Art*, 6 AM. CHEM. SOC'Y MED. CHEMISTRY LETTERS 364, 364 (2015).

14. *See* Andrew V. Trask, *"Obvious to Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2626, 2650–51 (2008) (noting that the Federal Circuit refused to equate "unpredictability with nonobviousness").

15. *See* W. Nicholson Price II, *The Cost of Novelty*, 120 COLUM. L. REV. 769, 774 (2020).

16. *See* David Dranove, Craig Garthwaite & Manuel Hermosilla, *Pharmaceutical Profits and the Social Value of Innovation* 3 (Nat'l Bureau of Econ. Rsch., Working Paper No. 20212, 2014), https://www.nber.org/papers/w20212 [https://perma.cc/U2D8-EZ9N].

17. *See id.*

18. *See generally* ROBERT P. MERGES, AMERICAN PATENT LAW: A BUSINESS AND ECONOMIC HISTORY (2023).

19. *See infra* Part III; *see also, e.g.*, INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, ADDRESSING PATENT THICKETS TO IMPROVE COMPETITION AND LOWER PRESCRIPTION DRUG PRICES 5 (2023). I-MAK proposes a higher standard of nonobviousness be met by patents on incremental improvements, such as new uses for the existing patented drug. *Id.*

I. THE VULNERABILITY OF INCREMENTAL R&D TO OBVIOUSNESS CHALLENGES

Pharmaceutical and biotechnological companies create drugs and biologics, respectively.[20] Some companies rely heavily on incremental R&D by which teams of skilled scientific researchers and technicians systemically apply known techniques to improve the value of existing products.[21] Generally, patent law does not reward systematic improvements that could be accomplished by any person having ordinary skill in the art (PHOSITA).[22]

When a patent is challenged, the courts or the USPTO, depending on the forum, must investigate what was known in the art and whether the invention was obvious in that context.[23] The burden on these reviewing bodies to understand scientific innovation is heavy, and Part I.A begins with a taste of the requisite background knowledge. Part I.B explains how courts and the USPTO assess obviousness generally, and Part I.C examines the unique challenges faced by pharmaceutical and biotechnological companies that have incrementally improved existing products. Finally, Part I.D summarizes how a patentee can rebut a prima facie case of obviousness using objective evidence.

A. The Regulatory Framework Behind Pharmaceutical and Biotechnological R&D

Part I.A.1 defines the relevant products to facilitate interpretation of the nonobviousness standard as it applies to pharmaceutical and biotechnological R&D. Part I.A.2 describes the parts of a patent and the challenges faced by patentees. Part I.A.3 summarizes government regulations of R&D.

1. Drugs and Biologics

Drugs are substances that alter biological systems and are used in the "diagnosis, cure, mitigation, treatment, or prevention of disease."[24] A drug's effects on the human body depend on a number of factors that are difficult to predict and control.[25] First, drugs can be administered in different ways, such as via injection or oral administration.[26] Once in the body, the active

20. *See infra* Part I.A.1.

21. *See* CONG. BUDGET OFF., RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 3 (2021) (suggesting that smaller companies focus on developing entirely new products that can be sold to larger companies, whereas larger companies focus on incremental R&D).

22. *See infra* Part I.B.

23. *See infra* Part I.B; *see also* Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17–18 (1966).

24. U.S. DEP'T OF HEALTH & HUM. SERVS., FOOD & DRUG ADMIN., CLASSIFICATION OF PRODUCTS AS DRUGS AND DEVICES & ADDITIONAL PRODUCT CLASSIFICATION ISSUES: GUIDANCE FOR INDUSTRY AND FDA STAFF 5 (2017).

25. *See* ERIC J. NESTLER, STEVEN E. HYMAN, DAVID M. HOLTZMAN & ROBERT C. MALENA, MOLECULAR NEUROPHARMACOLOGY: A FOUNDATION FOR CLINICAL NEUROSCIENCE 6 (3d ed. 2015).

26. *See id.*

ingredient[27] needs to reach its target without breaking down, a more difficult task for an orally administered drug.[28] Often, it reaches unintended targets and causes side effects.[29] Genetic differences can interfere with these processes and further limit the drug's efficacy.[30] Drugs have different effects on different bodies and even different effects over time in the same body.[31] The discovery of an active ingredient with therapeutic potential is just one step in an R&D marathon.[32]

Biologics, on the other hand, are isolated from endogenous sources—substances naturally occurring in humans, animals, or microorganisms.[33] In contrast to drugs, which are small molecules, biologics are larger and more structurally complex.[34] Biologics typically induce long-term changes that help the body fight the ailment itself.[35] Therefore, although a biologic may target similar systems, its effects may last longer and facilitate treatments of previously untreatable problems.[36] For example, the drug Revlimid®[37] and the biologic Humira®[38] both regulate the immune system by inhibiting a

27. *Id.* A drug is more than its active ingredient; drugs can be differentiated by their formulations, which are the mediums through which active ingredients are delivered, such as the solution injected. *See* Hao Zhong, Ging Chan, Yuanjia Hu, Hao Hu & Defang Ouyang, *A Comprehensive Map of FDA-Approved Pharmaceutical Products*, 10 PHARMS. 263, 263 (2018).

28. *See* NESTLER ET AL., *supra* note 25, at 6–7.

29. *See id.*

30. *See id.*

31. *See id.*

32. *See id.*

33. *See* Katelijne van de Vooren, Alessandro Curto & Livio Garattini, Editorial, *Biosimilar Versus Generic Drugs: Same But Different?*, 13 APPLIED HEALTH ECON. HEALTH POL'Y 125, 125–27 (2015), https://doi.org/10.1007/s40258-015-0154-9 [https://perma.cc/5ET5-N6SL].

34. *See* Anand N. Malaviya & Narinder K. Mehra, *A Fascinating Story of the Discovery & Development of Biologicals for Use in Clinical Medicine*, 148 INDIAN J. OF MED. RSCH. 263, 263 (2018).

35. Antitoxin treatments, such as that used against diphtheria, have existed since the late 1880s. *See id.* at 266. Vaccines are another well-known group of biologics. *See generally* Sonal Gupta & Sabine Pellett, *Recent Developments in Vaccine Design: From Live Vaccines to Recombinant Toxin Vaccines*, 15 TOXINS (BASEL) 563 (2023). The polio vaccines, for example, use an inactivated or weakened version of the virus to jump-start the body's own immune response. *Id.* at 564.

36. Thomas Morrow, *Defining the Difference: What Makes Biologics Unique*, 1 BIOTECHNOLOGY HEALTHCARE 24, 24 (2004). These bigger biological products are also more expensive to produce at large scale and cost substantially more to the patient per dose. *Id.* at 28. Two injections of Humira® can cost over $6,000 without insurance. *How Much Does Humira Cost Without Insurance?*, DRUGS.COM, https://www.drugs.com/medical-answers/humira-cost-without-insurance-3537595/ [https://perma.cc/E3HB-WQH3] (last visited Feb. 9, 2024). AbbVie made over $16 billion from Humira® in 2020 and it remains the world's best-selling drug. Jeffrey Wu & Claire Wan-Chiung Cheng, *Into the Woods: A Biologic Patent Thicket Analysis*, 19 CHI.-KENT J. INTELL. PROP. 93, 102 (2020).

37. CELGENE CORP., REVLIMID® (LENALIDOMIDE) CAPSULES: PACKAGE INSERT (2005), https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021880s064lbl.pdf.

38. ABBVIE, INC., HUMIRA® (ADALIMUMAB) INJECTION: PACKAGE INSERT (2002), https://www.rxabbvie.com/pdf/humira.pdf.

protein called tumor necrosis factor alpha (TNFα).[39] Revlimid® is administered orally and only lasts a few hours,[40] whereas Humira® is an injectable antibody and can last about two weeks.[41] Revlimid® is used primarily to treat multiple sclerosis, whereas Humira® is used to treat a number of previously untreatable conditions, including Crohn's disease.[42] However, the Humira® molecule is also about six hundred times heavier than that of Revlimid®, and a bigger, more complex product is more likely to have unpredictable side effects.[43]

Innovation in the pharmaceutical and biotechnological industries often arises through incremental improvements.[44] Drugs and biologics can be altered to create derivative products that have greater therapeutical potential.[45] Minor improvements of a small molecule drug create what is known as a "me-too" drug,[46] whereas improving a biologic creates a biosimilar.[47]

On the one hand, structural changes to a small molecule drug can improve its efficacy and stability.[48] On the other hand, biologics can be so large that they struggle to access their bodily targets; for example, they may be too large to get past the barrier that protects the brain.[49] Improvements to noninvasive delivery methods for biologics—such as methods to improve their capability to pass the blood-brain barrier—expand biologics' value to previously untreatable neurological disorders.[50]

Companies also modify drug and biologic formulations—the mediums through which active ingredients are delivered, such as the solution injected—to improve drug stability and shelf life.[51] These derivative products are not inconsequential; for example, although the MS Contin tablet was derived from a well-known active compound, morphine, a slow-release

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39. *See* Magda Melchert & Alan List, *The Thalidomide Saga*, 39 INT'L J. BIOCHEMISTRY & CELL BIOLOGY 1489, 1491 (2007); *see also* Alon D. Levin, Manon E. Wildenberg & Gijs R. van den Brink, *Mechanism of Action of Anti-TNF Therapy in Inflammatory Bowel Disease*, 10 J. CROHN'S & COLITIS 989, 992 (2016).

40. *See* CELGENE CORP., *supra* note 37.

41. *See* ABBVIE, INC., *supra* note 38.

42. *See* Levin et al., *supra* note 39, at 989.

43. *See* Liang Zhao, Tian-hua Ren & Diane D. Wang, *Clinical Pharmacology Considerations in Biologics Development*, 33 ACTA PHARMACOLOGICA SINICA 1339, 1340 (2012).

44. *See infra* Part II.A.2.

45. *See* GLOBERMAN & LYBECKER, *supra* note 3, at 25.

46. *See generally* Jeffrey Aronson & Richard Green, *Me-Too Pharmaceutical Products: History, Definitions, Examples, and Relevance to Drug Shortages and Essential Medicines Lists*, 86 BRIT. J. CLINICAL PHARMACOLOGY 2114 (2020).

47. *See* Victor L. Van de Wiele, Reed F. Beall, Aaron S. Kesselheim & Ameet Sarpatwari, *The Characteristics of Patents Impacting Availability of Biosimilars*, 40 NATURE BIOTECHNOLOGY 22, 22 (2022).

48. *See* Dranove et al., *supra* note 16, at 4.

49. Jason M. Lajoie & Eric V. Shusta, *Targeting Receptor-Mediated Transport for Delivery of Biologics Across the Blood-Brain Barrier*, 55 ANN. REV. PHARMACOLOGY & TOXICOLOGY 613, 613 (2015).

50. *Id.*

51. U.S. Patent No. 9,750,808 B2 (filed Jan. 27, 2017).

oral formulation meant patients no longer needed to be attached to a drip or injected at the hospital.[52]

2. Patents

Patents protect useful, novel, and nonobvious inventions.[53] The entity that examines whether an invention meets these qualifications is the USPTO,[54] which applies the guidelines compiled in the Manual of Patent Examining Procedure (MPEP).[55] The process of arguing to the USPTO that a patent meets the necessary criteria is called patent prosecution.[56] In addition to the three validity requirements, a patent must satisfy the "enablement" requirement—it must describe the claimed invention in sufficient detail to "enable any person skilled in the art . . . to make and use" the invention, such that others will be able to recreate it when the patent expires.[57] A patent includes "claims," which describe the substance and scope of the invention, such as the active ingredient, the dose, or a method of using the drug to treat a specific disease.[58]

During the nineteenth and early twentieth centuries, patents contained few claims.[59] A 1924 patent obtained for an axe had only two claims, one for each type of axe described and drawn.[60] In contrast, the 1997 patent on Revlimid® for use in reducing TNFα had ten claims, each providing a slightly modified compound.[61] The 2014 patent on a new indication (i.e., using the same drug to treat a different disease)[62] for Revlimid® had twenty-four claims covering the method of treating mantle cell lymphoma with different

52. *See* RHODES PHARM. L.P., MS CONTIN® (MORPHINE SULFATE EXTENDED-RELEASE) TABLETS: PACKAGE INSERT (1941), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019516s053s054lbl.pdf.

53. 35 U.S.C. §§ 101–103. Valid patents must satisfy three criteria: (1) novelty, (2) nonobviousness, and (3) usefulness. *Id.*

54. The USPTO is empowered by Congress to establish rules and regulations for its conduct, which are published in Title 37 of the Code of Federal Regulations. *See generally* 37 C.F.R. §§ 1–199 (2024).

55. MPEP (9th ed. Rev. 7, Feb. 2023).

56. *Id.* § 601; *see also* 35 U.S.C. § 111. Patent prosecution begins with an application that contains a title, specification, abstract, claims, and drawings or chemical diagrams, if they are necessary to understand the description. *Id.*

57. 35 U.S.C. § 112. The enablement requirement is heavily related to the "written description requirement," which states that the inventor must use sufficient detail in describing the invention. *See id.*

58. *Id.* § 111. Claims appear at the end of the specification in numbered paragraphs and describe what the inventor claims as their own product. 1 ROBERT A. MATTHEWS, JR., ANNOTATED PAT. DIG. § 1:24.

59. *See* J. Jonas Anderson & Peter S. Menell, *Informal Deference: A Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 NW. U. L. REV. 1, 13 (2014).

60. U.S. Patent No. 1,504,644 (filed Oct. 14, 1922).

61. U.S. Patent No. 5,635,517 (filed July 24, 1996).

62. *See Drugs@FDA Glossary of Terms*, U.S. FDA (Nov. 14, 2017), https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms [https://perma.cc/43QF-AR3K].

doses (5–25 mg), routes of administration (e.g., oral and intravenous infusion), and second active agents (for combination therapy).[63]

Claims become more elaborate as technology advances.[64] Although a company may want broad claims (e.g., all drugs that target TNFα), too much breadth can overlap with existing products and fail the novelty and nonobviousness requirements.[65] If claims are sufficiently detailed and narrow, then the patent owner's exclusive market is limited, but the likelihood of overlapping with existing protected inventions is comparatively low.[66]

Patentees in unpredictable fields must describe their inventions in greater detail and construe claims narrowly to protect future researchers from the burdens of "undue experimentation."[67] The unpredictable arts include chemistry, pharmacology, and biotechnology[68]—fields that are confounded by so many variables that it is impossible for anyone technically skilled in the art to know with certainty how those variables will interact to produce the intended results.[69] As early as 1950, Justice Robert H. Jackson noted that when several variables need to be combined in the chemical sciences, that combination may "take on some new quality or function from being brought into concert."[70] The USPTO similarly acknowledges that the burden of enabling an invention necessarily differs between predictable and unpredictable arts.[71]

After a patent is approved, its validity can still be scrutinized by the Patent Trial and Appeal Board (PTAB), district courts, and the Federal Circuit.[72] Patent validity can be challenged (1) by defendants in infringement lawsuits[73] or (2) by third parties asking the PTAB to review a USPTO decision granting a patent.[74] Third parties can petition the PTAB for inter partes review of a patent within nine months, challenging the patentability on novelty or nonobviousness grounds.[75] The PTAB has discretion to review a patent if the judges believe there is a "reasonable likelihood" that the

63. U.S. Patent No. 8,741,929 B2 (filed Nov. 19, 2009).

64. *See* MERGES, *supra* note 18, at 165.

65. *See* PETER S. MENELL, MARK A. LEMLEY, ROBERT P. MERGES & SHYAMKRISHNA BALGANESH, INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE 173, 230 (2023).

66. *See id.*

67. *In re* Wands, 858 F.2d 731, 736 (Fed. Cir. 1988).

68. *See* Tostmann, *supra* note 13, at 364. The predictable arts include mechanical and electrical engineering. *Id.*

69. *See* MPEP § 2164.03 (9th ed. Rev. 7, Feb. 2023) ("If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.").

70. Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp., 340 U.S. 147, 152 (1950).

71. MPEP § 2164.03.

72. *See, e.g.*, Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007); Mylan Pharms. Inc. v. Novo Nordisk a/s, No. IPR2023-00723, 2023 WL 6623324 (P.T.A.B. Oct. 2, 2023); *see also Inter Partes Review*, U.S. PAT. & TRADEMARK OFF. (Oct. 10, 2022), https://www.uspto.gov/patents/ptab/trials/inter-partes-review [https://perma.cc/6HFD-YUPG].

73. 35 U.S.C. § 282(b).

74. *See, e.g.*, *Pfizer*, 480 F.3d 1348; *Mylan*, 2023 WL 6623324.

75. 35 U.S.C. § 311.

petitioner can succeed in invalidating at least one claim.[76] Unfortunately for patentees, the PTAB is increasingly unlikely to deny patent review.[77] The "institution" rate has increased over the past three years and is now 70 percent.[78] The parties challenging patent validity are typically competitors that produce identical (or nearly identical) versions at lower prices,[79] known as "generic" drugs and "biosimilar" biologics.[80] Generics comprise 90 percent of the U.S. prescription market.[81] Biosimilars, however, are more difficult and expensive to produce, and their R&D requires substantial investment.[82] Biosimilars only comprise about 20 percent of the U.S. biologics market.[83]

3. Government Regulations

To reach the market, all drugs and biologics must obtain U.S. Food and Drug Administration (FDA) approval, an expensive and demanding

76. 37 C.F.R. § 1.923 (2024).

77. *See* Trenton Ward & Nicholas Cerulli, *Trending at the PTAB: Fintiv Is Alive, but with Way Less Zip*, LAW360 (Mar. 3, 2023, 2:53 PM), https://www.law360.com/articles/1582265/trending-at-the-ptab-fintiv-is-alive-but-with-way-less-zip# [https://perma.cc/5TRT-V5P7].

78. *Id.*

79. Nora Xu, *AIA Proceedings: A Prescription for Accelerating the Availability of Generic Drugs*, 66 EMORY L.J. 1007, 1021 (2017).

80. *See* Wu & Cheng, *supra* note 36, at 107–08. Competition often involves major companies, partially because of the expense of biosimilar production. *Id.* For example, Humira® interchangeable biosimilars are being introduced by Pfizer and Boehringer Ingelheim Pharmaceuticals, as their patents expired in 2023. *Purple Book Database of Licensed Biological Products*, U.S. FOOD & DRUG ADMIN. https://purplebooksearch.fda.gov/results?query=adalimumab&title=Humira [https://perma.cc/R92T-6PCD] (last visited Feb. 9, 2024).

81. Colleen Becker, *Decreasing Drug Costs Through Generics and Biosimilars*, NAT'L CONF. STATE LEGISLATURES (Jan. 21, 2022), https://www.ncsl.org/health/decreasing-drug-costs-through-generics-and-biosimilars [https://perma.cc/534G-9C9X]. Congress incentivized patent challenges by enacting the Hatch-Waxman Act. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of the U.S.C.). Before the Hatch-Waxman Act, generic drugs made up less than 20 percent of the drug market. *See* Xu, *supra* note 79, at 1011–12. The Biologics Price Competition and Innovation Act ("BPCI Act"), 42 U.S.C. § 262, functions similarly for biosimilars and encourages the patentee and challenger into a series of pre-litigation negotiations commonly called the "patent dance" that promotes settlement. *See also* Lindsay Kelly, *Biologics in the Practice of Law*, 39 HARV. J.L. & PUB. POL'Y 21, 25 (2016).

82. *See* Wu & Cheng, *supra* note 36, at 103. Although generics must be "bioequivalent" to the original product, biosimilars are held to a lower standard. *Id.* The manufacturing process for biologics is often a protected trade secret, which forces companies to rely on reverse engineering. *Id.* at 107–08. If a company manages to produce an equivalent biologic, however, then it obtains the status of "interchangeable biosimilar." *Biosimilar and Interchangeable Biologics: More Treatment Choices*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices [https://perma.cc/C657-LPX9] (Aug. 17, 2023).

83. *Biosimilars in the United States*, IQVIA INST. (Jan. 21, 2023), https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/biosimilars-in-the-united-states-2023-2027 [https://perma.cc/U9EG-VAP7].

process.[84] Over the past two decades, pharmaceutical companies spent nearly one billion dollars per drug in obtaining FDA approval,[85] and only about half of "big" companies realized sufficient profits to compensate for their R&D costs.[86] Only thirty-seven new drugs received FDA approval in 2022, down from fifty-one in 2021.[87] Sixteen of the big companies spent over six billion dollars per drug approval on average over the last two decades.[88] Of those companies, seven had negative R&D productivity,[89] compensating for those losses through licensing and acquisitions of smaller companies, such as those spun off from academic institutions.[90] Of the new drugs approved between 2015 and 2021, only about one quarter were developed internally.[91]

Incremental improvements to existing drugs[92] and biologics[93] incur regulatory advantages. Derivative products are more likely to obtain FDA approval[94] in a speedier process.[95] The timelines for obtaining patent protection and FDA approval, however, often come into conflict. When

84. Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 27 (2016) (calculating rising expenses of drug testing). Clinical studies occur in phases. *Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/drug-development-process/step-3-clinical-research [https://perma.cc/2JEL-FWVD] (Jan. 4, 2018). Phase I occurs typically in healthy human volunteers to demonstrate safety. *Id.* Phase II studies are larger (100–300 volunteers) and suggest effectiveness of the drug. *Id.* Phase III "pivotal" studies are large (300–3,000 volunteers) and well-controlled studies that monitor long-term effects of the drug. *Id.*

85. *See* Olivier J. Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018*, 323 JAMA 844, 850 (2020).

86. *See* Alexander Schuhmacher, Markus Hinder, Alexander von Stegmann und Stein, Dominik Hartl & Oliver Gassmann, *Analysis of Pharma R&D Productivity—A New Perspective Needed*, DRUG DISCOVERY TODAY, Oct. 2023, at 2 (defining "big pharma" as "the largest and globally active research-based pharmaceutical firms that cover the entire value chain from drug discovery to development and commercialization of new drugs").

87. *New Drug Approvals for 2022*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2022 [https://perma.cc/CS23-3CHV] (Feb. 1, 2024).

88. *See id.*

89. *See* Schuhmacher et al., *supra* note 86, at 5.

90. *Id.*; *see also* Alexander Schuhmacher, Markus Hinder, Alexander Dodel, Oliver Gassmann & Dominik Hartl, *Investigating the Origins of Recent Pharmaceutical Innovation*, 22 NATURE REVS. DRUG DISCOVERY 781, 781 (2023).

91. *See* Schuhmacher et al., *supra* note 90, at 781.

92. *See* Aronson & Green, *supra* note 46, at 2117.

93. *See* Miriam Fontanillo, Boris Körs & Alex Monnard, *Three Imperatives for R&D in Biosimilars*, MCKINSEY & CO. (Aug. 19, 2022), https://www.mckinsey.com/industries/life-sciences/our-insights/three-imperatives-for-r-and-d-in-biosimilars [https://perma.cc/R92Y-NEBD].

94. *See* Joshua Krieger, Danielle Li & Dimitris Papanikolaou, *Missing Novelty in Drug Development*, 35 REV. FIN. STUD. 636, 638 (2020) ("[A] one-standard-deviation increase in novelty is associated with a 24% decrease in the likelihood that a drug candidate receives regulatory approval from the FDA.").

95. *See* Fontanillo et al., *supra* note 93; *see also Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review [https://perma.cc/R7A6-GRSU] (June 12, 2023).

seeking patent protection, patentees must support the contention that their invention works as intended with some concrete data; however, they also must apply before (or within one year after) the research is published, such as in a research article.[96] This means that they must obtain patents before obtaining FDA approval.[97] The products that survive FDA scrutiny likely spend ten years in development after patenting, thereby missing out on years of exclusive market access.[98] Derivative uses of existing drugs, however, benefit from prior clinical testing completed on the drug, saving companies millions in R&D costs.[99] In addition, under the Biologics Price Competition and Innovation Act of 2009[100] ("BPCI Act"), the FDA can grant biosimilars access to an abbreviated approval pathway.

B. Obviousness Challenges to Patents on Derivative Products

Nonobviousness was not always a statutory requirement for patentability. It was born in case law, ultimately codified in 1953 under § 103[101]—the nonobviousness requirement that still controls today.[102] The modern statute requires that the advancement must not be obvious to a PHOSITA at the time of invention:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.[103]

The Supreme Court in *Graham v. John Deere Company of Kansas City*[104] set forth the inquiry for obviousness, which courts and the PTAB use today. Factfinders must determine (1) the scope and content of the prior art, (2) the level of ordinary skill in the art at the time the invention was made, and (3) differences between the claimed invention and prior art.[105] Possible prior art references include applications, patents, and publications (including textbooks and treatises) available to the public prior to the effective filing date.[106] Those references "analogous . . . to the claimed invention" are

96. *See* 35 U.S.C. § 102(b)(1).
97. Dmitry Karshtedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 IOWA L. REV. 1129, 1138 (2019).
98. *See* Michael Enzo Furrow, *Pharmaceutical Patent Life-Cycle Management After* KSR v. Teleflex, 63 FOOD & DRUG L.J. 275, 300 (2008). Note that patents generally last for a term of twenty years. 35 U.S.C. § 154(a)(2).
99. *See* Curtis Chong & David Sullivan Jr., *New Uses for Old Drugs*, 448 NATURE 645, 645 (2007).
100. 42 U.S.C. § 262.
101. *See* 35 U.S.C. § 103.
102. *Id.*
103. *Id.*
104. 383 U.S. 1, 19 (1966).
105. *See id.* at 17–18.
106. *See* 35 U.S.C. § 102(a).

included in the analysis.[107] Part I.B.1 describes how references are designated as analogous. Part I.B.2 characterizes the perspective from which prior art is analyzed, and Part I.B.3 summarizes the modern standard for nonobviousness.

1. Scope of the Prior Art

The scope of analogous art is determined using one of two tests described by the Federal Circuit in *In re Bigio*[108]: the "field of endeavor" test or the "reasonably pertinent" test.[109] Prior art is generally limited to references within the inventor's "field of endeavor," those that satisfy the first test.[110] Courts "do not charge a [PHOSITA] to know all arts" but will assume that they know all of the art within their own field-of-endeavor.[111] If prior art from a different field fails the first test, it may be still be analogous if it is "reasonably pertinent" to the problem that the invention is meant to solve.[112] Courts will assume that an inventor would have reviewed a reference that, because of its subject matter, would have naturally come to the inventor's attention.[113] For example, an inventor designing the hinge attachment for a laptop screen would logically consult other hinge designs, so invalidating prior art references may include kitchen cabinet hinges.[114] Patentees do not need to explicitly state the problem they intended to solve; the reviewing body has discretion in determining the problem.[115]

Inventors cannot patent the same product twice.[116] Moreover, an inventor cannot obtain multiple patents on a single invention by making minor changes to the claims.[117] The judicial doctrine known as Obviousness-Type Double Patenting (OTDP) stipulates that some inventions are "so alike that granting both exclusive rights would effectively extend the life of patent protection."[118] In cases concerning minor changes to claims, courts (1) construe the claims of both patents and (2) determine "whether the differences render the claims patentably distinct."[119] The second step of the

107. MPEP § 2141.01(a) (9th ed. Rev. 7, Feb. 2023).
108. 381 F.3d 1320 (Fed. Cir. 2004).
109. *Id.* at 1325.
110. *Id.*
111. *See* Netflix, Inc. v. DivX, LLC, 80 F.4th 1352, 1358 (Fed. Cir. 2023); *see also* Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) (clarifying that the actual level of skill possessed by the inventor is not relevant). A party alleging the invalidity of a patent does not need to explicitly define the field, and courts have latitude to determine the breadth of the field. *See id.*
112. *Bigio*, 381 F.3d at 1325.
113. *See id.*
114. *See In re* Paulsen, 30 F.3d 1475, 1481 (Fed. Cir. 1994).
115. *See Netflix*, 80 F.4th at 1362 (finding no clear error in the PTAB's use of the "specification, claims, and prosecution history" to determine the problem).
116. *See* 35 U.S.C. § 102.
117. *See* AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366, 1379 (Fed. Cir. 2014).
118. Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1373 (Fed. Cir. 2005).
119. *AbbVie*, 764 F.3d at 1374 (quoting Sun Pharm. Indus., Ltd. v. Eli Lilly & Co., 611 F.3d 1381, 1385 (Fed. Cir. 2010)). Claim construction is the process of interpreting the scope

OTDP inquiry relies on "the law of obviousness generally" to ensure that a patentee is not extending the patent's term by making minor, immaterial variants.[120] OTDP does not necessarily preclude patenting, but the USPTO requires terminal disclaimers that end the lifespan of the secondary patent when the primary patent expires.[121] For example, if a patentee claims a broad class of compounds, any subsequent claims over a compound within that class is OTDP, so the patentee would need to add a terminal disclaimer that synchronizes their expiration dates.[122]

2. Ordinary Skill in the Art

Nonobviousness is evaluated from the perspective of a PHOSITA at the time the patentee effectively filed their application.[123] Factors relevant to this analysis include the "type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field."[124] This determination serves as the "prism or lens through which a judge, jury, or the [PTAB] views the prior art and the claimed invention."[125] The factfinder is encouraged to preserve objectivity and resist inserting their own knowledge or hindsight into the analysis.[126] "A less sophisticated level of skill generally favors a determination of nonobviousness . . . while a higher level of skill favors the reverse."[127] In the pharmaceutical and biotechnology sciences, a PHOSITA would have at least a Bachelor's degree in biology, chemistry, pharmacy, or a related discipline and about five years of research or clinical experience in the relevant field.[128] For example, for evaluating biologics, a PHOSITA has spent about five years researching antibodies or viral vectors for gene delivery.[129]

3. The Flexible "Obvious to Try" Analysis

To determine if the invention was "obvious to try," the court or PTAB combines the teachings of the prior art references and compares them to the claims.[130] When the prior art provides the necessary teachings, the invention

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of patent claims from the perspective of a PHOSITA. Phillips v. AWH Corp., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005).

120. *Phillips*, 415 F.3d at 1378.

121. *See* MPEP § 804.02 (9th ed. Rev. 7, Feb. 2023).

122. *See AbbVie*, 764 F.3d at 1379.

123. 35 U.S.C. § 103. The effective filing date is typically the actual filing date, but there are some exceptions, such as if the patentee filed a continuation of an earlier application. *See* MPEP § 2152.01 (9th ed. Rev. 7, Feb. 2023).

124. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed. Cir. 1986).

125. Okajima v. Bourdeau, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

126. *See id.*

127. *See* Innovention Toys, LLC v. MGA Ent., Inc., 637 F.3d 1314, 1323 (Fed. Cir. 2011).

128. Novartis Gene Therapies Inc. & Novartis Pharm. Corp. v. Genzyme Corp., No. IPR2023-00609, at 12 (P.T.A.B. Aug. 30, 2023).

129. *See id.*

130. *See* MPEP § 2141 (9th ed. Rev. 7, Feb. 2023).

is the inevitable consequence of a PHOSITA continuing to experiment in the field—in other words, the invention "flow[s] naturally from the teachings of the prior art."[131] As scientific progress expanded the breadth of prior art, the notion that an experiment could be "obvious to try" briefly fell out of favor,[132] but the U.S. Supreme Court revived the inquiry in *KSR International v. Teleflex*.[133] Echoing earlier opinions, the Court held that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."[134] The patent challenged in *KSR* covered a product of mechanical engineering that connected an automatic sensor to an automobile break. The Court found that the patentee relied on a "predictable use of prior art,"[135] specifically, two patents on an adjustable pedal and a method for mounting a brake sensor.[136] The *KSR* holding provided that a patent is obvious if there is evidence of (1) some motivating problem, which can include "design need" or "market demand," and (2) a "finite number of identified, predictable solutions" to try.[137]

For example, in the midst of the opioid crisis, the FDA publicly urged companies to develop a treatment for overdose that could be delivered quickly by inexperienced hands.[138] The FDA requested an intranasal formulation of naloxone (an opioid antagonist)[139] at a dose greater than 2 milligrams, given prior data that 2 milligrams were insufficient to be effective.[140] A company obtained a patent on a 4 milligram intranasal spray, marketed as NARCAN®.[141] Then, a generic manufacturer challenged the validity of the patent on the grounds that combined prior art rendered it obvious.[142] The challenger combined an existing patent disclosing spray applicators of opioid antagonists, a research article disclosing the efficacy of 2 milligrams of naloxone, and an existing patent disclosing a preservative that would prevent naloxone degradation.[143] The Federal Circuit held that the invention was obvious in view of the prior art because it "required no more than routine optimization" of variables within known ranges.[144]

131. *In re* Kepler, 132 F.2d 130, 133 (C.C.P.A. 1942).
132. *In re* Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988).
133. 550 U.S. 398, 399 (2007).
134. *Id.* at 416.
135. *Id.* at 417.
136. *Id.* at 411.
137. *Id.* at 402.
138. Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc., 25 F.4th 1354, 1361 (Fed. Cir. 2022).
139. *See* Kathleen Handal, Jay Schauben & Francine Salamone, *Naloxone*, 12 ANNALS EMERGENCY MED. 438, 438 (1983).
140. *Adapt Pharma*, 25 F.4th at 1361.
141. *Id.*
142. *Id.* at 1362.
143. *Id.* at 1362–63.
144. *Id.* at 1369.

C. Routine Optimization

The flexible, commonsense approach to obviousness set forth in *KSR* poses problems for the pharmaceutical and biotechnology industries. Since *KSR*, courts have generally asked (1) whether the prior art identifies problems that would motivate inventors to research solutions and (2) whether the prior art identifies variables that could be routinely optimized to solve these problems with a reasonable expectation of success.[145] In other words, inventions are obvious to try if the prior art identified both problems and predictable solutions.[146] Because incremental pharmaceutical and biotechnological R&D is problem-oriented, however, "the pharmaceutical industry may be particularly adversely impacted by application of an 'obvious to try' analysis."[147] Patents on derivative drugs are particularly vulnerable to rejection under the doctrine because they solve the flaws of existing products.[148] When such improvements rely on routine optimization of variables known to mediate drug or biologic efficacy and stability, these methods preclude patentability.[149] Routine optimization is manifested by experimentation with "result-effective variables," variables taught by the prior art to solve known problems.[150] If result-effective variables are identified, courts examine whether the prior art provides a finite and predictable number of options to try, such that modification of the variable was routine testing and verification.[151] Part I.C.1 describes when courts designate variables as result-effective, and Part I.C.2 examines how courts analyze these variables.

1. Identifying Result-Effective Variables

"[A]fter *KSR*, the presence of a known result-effective variable would be one, but not the only, motivation for a person of ordinary skill in the art to experiment to reach another workable product or process."[152] An optimized result-effective variable achieves a potential result recognized by the prior

145. *See* KSR Int'l Co. v. Teleflex. Inc., 550 U.S. 398, 421 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp.").

146. *See id.*

147. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1367 (Fed. Cir. 2007).

148. *See* Mark A. Lemley, *Expecting the Unexpected*, 92 NOTRE DAME L. REV. 1369, 1370 (2017) ("Patents likely to be affected by the obvious-to-try rule tend to be follow-on patents used to try to extend the life of expired patents on new chemical entities, not breakthrough drugs that require strong protection.").

149. *Pfizer*, 480 F.3d at 1367 (holding that whether the methodology is insufficient to qualify as inventive will depend "on the *particularized facts of* [the] *case*.").

150. *See* E.I. DuPont de Nemours & Co. v. Synvina C.V., 904 F.3d 996, 1003 (Fed. Cir. 2018).

151. *See id.* ("For decades, this court and its predecessor have recognized that 'where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'" (quoting *In re* Aller, 220 F.2d 454, 456 (C.C.P.A. 1955))).

152. MPEP § 2144.05(III)(C) (9th ed. Rev. 7, Feb. 2023).

art.[153] If the prior art discloses a relationship between a parameter and a desirable result, the optimization of that parameter to achieve the best result is not inventive.[154] For example, temperature is widely known to contribute to food expiration, so finding a refrigerator setting that best extends the freshness of a food item is not inventive.[155] Similarly, if prior art discloses a pH range and relates pH to drug stability, optimizing pH to stabilize a drug is not inventive.[156] Improvements to result-effective variables are merely optimizations within the skill of the art, not inventions.[157] Many of the variables relevant to R&D, including concentrations, pH values, and temperatures, have documented effects, making them result-effective.[158]

The requirements for a variable to qualify as result-effective are minimal. A variable will only fail to qualify if there is "no evidence in the record that the prior art recognized that particular parameter affected the result."[159] The prior art does not need to disclose experimental methods with which to optimize the variable.[160] The correlation between the variable and result does not need to be tight, meaning that the relationship does not need to surpass a threshold of predictability.[161] The recognition that the variable contributes to the result can be explicit or implied by the prior art.[162] Because the bar for result-effective variable recognition is low, patent owners must rebut the presence of routine optimization in their R&D.[163]

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153. *See* Wilensky, *supra* note 10, at 42.

154. *See* Ryan Pool, *Routine Optimization: A Performance Review*, 101 J. PAT. & TRADEMARK OFF. SOC'Y 390, 398 (2021) ("[T]he failure to teach any relationship between variable and property is not enough, but a 'comprehensive explication of the known relationships between the variables and the affected properties,' is not required to justify a prima facie case." (quoting *In re* Applied Materials, Inc., 692 F.3d 1289, 1297 (Fed. Cir. 2012))).

155. *See Are You Storing Food Safely?*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/consumers/consumer-updates/are-you-storing-food-safely [https://perma.cc/ULT9-XZJ3] (Jan. 18, 2023).

156. *See* Azurity Pharms., Inc. v. Alkem Labs. Ltd., 655 F. Supp. 3d 270, 284 (D. Del. 2023) (describing how pH is known to affect chemical stability, without identifying it as a result-effective variable); *see also* Eyenovia, Inc. v. Sydnexis, Inc., No. IPR2022-00384, at 46 (P.T.A.B. July 12, 2023) (finding "no dispute that pH is a result effective variable for the stability" of a solution).

157. *See Applied Materials*, 692 F.3d at 1295.

158. *See In re* Aller, 220 F.2d 454, 456 (C.C.P.A. 1955) ("Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification.").

159. *In re* Antonie, 559 F.2d 618, 620 (C.C.P.A. 1977).

160. *See Applied Materials*, 692 F.3d at 1297.

161. *See* E.I. DuPont de Nemours & Co. v. Synvina C.V., 904 F.3d 996, 1009 (Fed. Cir. 2018); *see also* Pioneer Pet Prods., LLC v. Oil-Dri Corp. of Am., No. IPR2022-00691, at 30 (P.T.A.B. Sept. 12, 2023) (rejecting petitioner's argument that surface area is not a result-effective variable because there is "no predictable correlation between surface area and clumpability" of kitty litter).

162. *See DuPont*, 904 F.3d at 1009; *Applied Materials*, 692 F.3d at 1297 ("A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective.").

163. *See, e.g.*, R.J. Reynolds Vapor Co. v. Philip Morris Prods. S.A., No. IPR2021-00585, at 45 (P.T.A.B. Sept. 8, 2022). If a petitioner asserts that routine optimization occurred, the patent owner may argue in rebuttal that variables could not have been routinely optimized

Because the result does not need to be explicitly disclosed, courts rely on external evidence interpreting the state of the art to determine whether prior art implicitly taught how to routinely optimize existing products.[164] Mere conclusory allegations that a variable was known to facilitate the claimed results are insufficient.[165] Expert testimony, on the other hand, is valuable. For example, in *E.I. DuPont de Nemours & Co. v. Synvina C.V.*,[166] the Federal Circuit relied on expert testimony showing that a PHOSITA would have expected manipulation of the variables—temperature and oxygen pressure—to increase their product yield.[167] The expert provided the intermediate logic—temperature and oxygen mediate reaction rate—that would have likely led a PHOSITA to make the necessary connection.[168]

2. Finding Optimization of Result-Effective Variables

The *KSR* "obvious to try" inquiry is therefore partly satisfied by the identification of problems and potential solutions, but only if a "reasonable expectation of success" exists.[169] Success is predictable if the prior art discloses a range of possible values within which to optimize a single variable.[170] If the prior art discloses a broad range of values, or "a finite number of identified, predictable solutions," then narrowing that range is merely routine optimization.[171] As a result, a showing that a patent owner narrowed a range of values disclosed by the prior art establishes a prima facie case of obviousness.[172] The prior art disclosure can often be broad, leaving inventors with the hefty task of subsequent experimentation.[173] However, the time and expense of routine optimization does not dissuade courts from finding obviousness.[174] Moreover, for pharmaceutical inquiries, the prior art

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because the prior art failed to identify them as result-effective, shifting the burden. *DuPont*, 904 F.3d at 1006.

164. *See, e.g.*, Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc., 25 F.4th 1354, 1731 (Fed. Cir. 2022); Genentech, Inc. v. Hospira, Inc., 946 F.3d 1333, 1340 (Fed. Cir. 2020) (giving more credibility to one expert over another); *DuPont*, 904 F.3d at 1009.

165. *See* Fluid Energy Grp. Ltd. v. Green Prods & Tech., LLC, No. IPR2021-00357, at 30 (P.T.A.B. July 5, 2022); *see also* Novartis Gene Therapies, Inc. & Novartis Pharms. Corp. v. Genzyme Corp., No. IPR2023-00609, at 23 (P.T.A.B. Aug. 30, 2023).

166. 904 F.3d 996 (Fed. Cir. 2018).

167. *Id.* at 1009.

168. *See id.*

169. *See* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1365–69 (Fed. Cir. 2007).

170. *See id.* at 1369.

171. KSR Int'l Co. v. Teleflex. Inc., 550 U.S. 398, 421 (2007).

172. *See In re* Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (suggesting that it is "[t]he normal desire of scientists or artisans to improve upon what is already generally known . . . to determine where in a disclosed set of percentage ranges is the optimum combination of percentages").

173. *Pfizer*, 480 F.3d at 1366.

174. *See id.* at 1367 ("This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably 'routine' to one of ordinary skill in the art."); *see also* Lemley, *supra* note 148, at 1391 (noting that "[p]atent law flirted with protecting things that are straightforward but expensive to develop in a series of biotechnology cases in the 1990s," but *KSR* facilitated reversals).

does not need to describe the same compound as the claims to preclude patent validity.[175] Ranges for structurally or functionally similar compounds can also establish obviousness.[176]

An experimenter optimizes a variable by narrowing a range of values disclosed by prior art.[177] For example, in *Amperex Technology v. Maxwell*,[178] the prior art disclosed an element's molar amount, called variable M^2, as between 0 and 0.5, whereas the claims identified a much narrower range between 0.002 and 0.05.[179] A prima facie case of obviousness was met because the claimed range for the result-effective variable, M^2 concentration, was optimized from that previously disclosed by the prior art, shifting the burden of showing nonobviousness to the patentee.[180] Although the 0 to 0.5 range was considerably broad and must have required extensive testing to narrow, expert testimony suggested that a PHOSITA would have started with the smallest value (zero) and routinely increased the molar amount to find the most effective range.[181] Therefore, in reaching the claimed narrowed range, the inventor only practiced "routine experimentation" by finding an effective range just beyond a molar amount of zero.[182]

Routine optimization may have occurred even if the claimed range borders with, but does not fully overlap, explicit ranges disclosed by prior art.[183] Factfinders can use intrinsic evidence (e.g., approximation language in the claims or specification) and extrinsic evidence (e.g., textbooks or expert testimony) to determine whether a PHOSITA would understand the ranges as overlapping.[184] The Federal Circuit "reject[s] any invitation to create a bright-line rule—either that language like 'precisely' or 'exactly' is always needed to avoid rounding or that the lack of approximation language, even when it may be found elsewhere in the claims, dictates a precise value."[185] Factfinders can therefore expand approximated ranges to encompass the claimed ranges.[186] Prior art ranges need only slightly overlap with or abut claimed ranges.[187] The Federal Circuit has found obviousness even when

175. *See* Valeant Pharms. Int'l Inc. v. Mylan Pharms. Inc., 955 F.3d 25, 32 (Fed. Cir. 2020).
176. *See id.*
177. Tom Brody, *Claims with Ranges, the Result-Effective Variable, and* In Re Applied Materials, 98 J. PAT. & TRADEMARK OFF. SOC'Y 618, 624 (2016).
178. No. IPR2021-01441 (P.T.A.B. Mar. 28, 2023).
179. *See id.* at 32.
180. *See id.*
181. *See id.* at 34.
182. *Id.* at 33.
183. *See* Brody, *supra* note 177, at 625.
184. *See* Actelion Pharms. Ltd. v. Mylan Pharms. Inc., 85 F.4th 1167, 1173–74 (Fed. Cir. 2023).
185. *Id.* at 1171.
186. *See* Azurity Pharms., Inc. v. Alkem Labs. Ltd., 655 F. Supp. 3d 270, 296 (D. Del. 2023) (finding pH of 3.3 to be "about 3").
187. *See In re* Woodruff, 919 F.2d 1575, 1577 (Fed. Cir. 1990).

ranges were merely "very close" to the claimed ranges.[188] On the other hand, "disclosure of very broad ranges may not invite routine optimization."[189] Some courts acknowledge that a PHOSITA's motivation to optimize a result-effective variable is limited if the prior art provides an overbroad range.[190]

The presence of multiple result-effective variables further complicates routine optimization but does not necessarily preclude a finding of nonobviousness.[191] "[F]or there to be a reasonable expectation of success, 'one must be motivated to do more than merely to vary all parameters or try each of the numerous possible choices until one possibly arrived at a successful result.'"[192] A PHOSITA is therefore not expected to test every possible combination to obtain the claimed invention.[193] However, *In re Applied Materials, Inc.*[194] held that combining multiple result-effective variables is not inherently beyond ordinary skill in the art, at least within the predictable art of mechanical engineering.[195] Applied Materials had altered the depth, width, and pitch of the grooves on its polishing pads, each within ranges disclosed by three prior art references.[196] The Federal Circuit found that the relationship between these variables and the overall performance was predictable.[197] The PTAB has similarly concluded that an invention that modifies multiple variables can still be obvious, at least within the context of mechanical engineering.[198]

D. Objective Indicia of Nonobviousness

A patentee can rebut a finding of obviousness by showing objective indicia of nonobviousness, or "secondary considerations."[199] The indicia serve as a "check against hindsight bias"[200] and keep attention focused on the state of the art at the time of filing.[201] These include commercial success, unexpected results, long felt but unmet need, failure of others to solve the

188. *See, e.g.*, Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 783 (Fed. Cir. 1985) (finding that 0.3 percent Mo and 0.8 percent Ni are close enough to 0.25 percent Mo and 0.75 percent Ni to create overlap).

189. E.I. DuPont de Nemours & Co. v. Synvina C.V., 904 F.3d 996, 1006 (Fed. Cir. 2018).

190. *See In re* Baird, 16 F.3d 380, 383 (Fed. Cir. 1994).

191. *In re* Applied Materials, Inc., 692 F.3d 1289, 1298 (Fed. Cir. 2012).

192. *See* R.J. Reynolds Vapor Co. v. Philip Morris Prods. S.A., No. IPR2021-00585, at 57 (P.T.A.B. Sept. 8, 2022) (quoting *In re* Stepan Co., 868 F.3d 1342, 1347 (Fed. Cir. 2017)).

193. *See id.*

194. 692 F.3d 1289 (Fed. Cir. 2012).

195. *See id.* at 1298.

196. *See id.*

197. *See id.* at 1297–98.

198. *See* Brunswick Corp. v. Volvo Penta of the Ams., LLC, No. IPR2020-01512, at 23 (P.T.A.B. Mar. 3, 2022) ("[W]e see no reason . . . that the *sheer number* of changes precludes a finding of obviousness, especially in the mechanical arts.").

199. Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17–18 (1966).

200. *In re* Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig., 676 F.3d 1063, 1078–79 (Fed. Cir. 2012).

201. *See* Natalie A. Thomas, *Secondary Considerations in Nonobviousness Analysis: The Use of Objective Indicia Following* KSR v. Teleflex, 86 N.Y.U. L. REV. 2070, 2102 (2011).

known problem, and copying.[202] Evidence that a drug or biologic is commercially successful or meets an unmet need suggests that, if the patentee's experiments were truly obvious, a competitor would have tried it already.[203] To make such a rebuttal, the patentee must demonstrate a nexus between the indicia and the claims.[204] For example, although a crush-resistant formulation of oxycodone was extremely profitable, the crush-resistant feature did not drive the profits.[205] Secondary considerations must be examined but may not be found meaningful.[206] The PTAB appears to be less friendly to objective indicia than the Federal Circuit, considering them minimally[207] and in vague terms.[208]

It is difficult for a patentee to show unexpected results when they have modified result-effective variables.[209] Unpredictability of the pharmaceutical and biotechnological sciences does not necessarily import unexpectedness.[210] For example, if a patentee adjusts pH to enhance stability, then improved stability is expected even if the patentee faced unpredictable problems during R&D.[211] If the patentee has narrowed a range

202. *See Graham*, 383 U.S. at 17–19; *see also* Volvo Penta of the Ams., LLC v. Brunswick Corp., 81 F.4th 1202, 1210 (Fed. Cir. 2023) ("A showing of nexus can be made in two ways: (1) via a presumption of nexus, or (2) via a showing that the evidence is a direct result of the unique characteristics of the claimed invention.").

203. *See* Amanda Wieker, *Secondary Considerations Should Be Given Increased Weight in Obviousness Inquiries Under 35 U.S.C. § 103 in the Post-*KSR v. Teleflex *World*, 17 FED. CIR. BAR J. 665, 675 (2008) (noting that commercial success was the most commonly invoked secondary consideration, at least prior to *KSR*).

204. *See, e.g.*, Purdue Pharma L.P. v. Accord Healthcare Inc., No. CV 20-1362, 2023 WL 2894939, at *12 (D. Del. Apr. 11, 2023); Azurity Pharms., Inc. v. Alkem Lab'ys Ltd., 655 F. Supp. 3d 270, 300 (D. Del.), *aff'd* No. 2023-1540, 2023 WL 5970784 (Fed. Cir. Sept. 14, 2023); Chemours Co. FC, LLC v. Daikin Indus., Ltd., 4 F.4th 1370, 1378 (Fed. Cir. 2021), *cert. denied*, 142 S. Ct. 1418 (2022).

205. *Purdue*, 2023 WL 2894939, at *12. The crush-resistant version effectively replaced the original in the marketplace, so the sales transferred. *Id.*

206. *See* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion.").

207. *See* Dani Kass, *Judge O'Malley Thinks Fed. Circ. Could Be Back This Summer*, LAW360 (Mar. 25, 2021, 9:43 PM EDT), https://www.law360.com/articles/1342597/judge-o-malley-thinks-fed-circ-could-be-back-this-summer [https://perma.cc/RGJ8-AP6P] (explaining that Federal Circuit Judge Kathleen M. O'Malley "expressed 'frustration' about how the [PTAB] disregards objective indicia of nonobviousness").

208. *See* Volvo Penta of the Ams., LLC v. Brunswick Corp., 81 F.4th 1202, 1214 (Fed. Cir. 2023) ("[T]he Board assigned industry praise, commercial success, and copying all 'some weight.' The Board did not explain why it gave these three factors the same weight . . . . Although 'some weight' may not always be ambiguous, it is in this context.").

209. *See* Eyenovia, Inc. v. Sydnexis, Inc., No. IPR2022-00384, at 47 (P.T.A.B. July 13, 2023) (finding an unexpected problem that the patentee had to solve unimportant because the results were expected).

210. *See id.*

211. *Id.* (holding that, even though the patentee faced unexpected problems working with a low dose of atropine, "the result of using a buffer, pH stability for the range, was not unexpected"); *see also In re* Aller, 220 F.2d 454, 456 (C.C.P.A. 1955) (noting that changes in variables such as temperature and concentration "may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art").

disclosed by prior art,[212] they must provide "evidence that the claimed range is 'critical' because it 'achieves unexpected results.'"[213] Such evidence must include factual data, not just "conclusory"[214] or "speculative"[215] statements. Because nonobvious inventions provide "some superior property or advantage"[216] above the closest prior art, the patentee can demonstrate criticality by specifying values within the range that failed to produce the claimed result.[217]

In summary, pharmaceutical and biotechnological R&D often relies on incremental advancements, and patents protecting these products are vulnerable to obviousness challenges. Because the scrutiny applied to patents can mediate the expected value of incremental R&D, Part II examines arguments for and against patent protection of derivative products.

II. VIEWS ON THE PATENTABILITY OF INCREMENTAL R&D

R&D can be either incremental and improve existing products, or disruptive and change the course of the field.[218] Although patents on derivate products are vulnerable to invalidation under the routine optimization doctrine,[219] companies invest heavily in incremental R&D.[220] Patent law is meant to promote scientific progress, but scholars and critics diverge in how narrowly they define progress.[221] Some argue that patent law should reward incremental R&D because it has immense cumulative value for the public and is notoriously unpredictable.[222] Others argue that incremental R&D is not the kind of innovation that patent law incentivizes;[223] instead, patents should protect disruptive R&D.[224] They suggest that low standards for patentability create opportunities for pharmaceutical and biotechnology companies to exploit the patent system and keep competitors out of the

212. *See supra* Part I.C.2.

213. *In re* Applied Materials, Inc., 692 F.3d 1289, 1297 (Fed. Cir. 2012) (quoting *In re* Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

214. Amperex Tech. Ltd. v. Maxwell, Ltd., No. IPR2021-01441, at 37 (P.T.A.B. Mar. 28, 2023).

215. Purdue Pharma L.P. v. Accord Healthcare Inc., No. 20-1362, 2023 WL 2894939, at *21 (D. Del. Apr. 11, 2023).

216. *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995).

217. *See* Brody, *supra* note 177, at 629.

218. *See* Max Kozlov, *'Disruptive' Science Has Declined—Even as Papers Proliferate*, 613 NATURE 225, 225 (2023).

219. *See supra* Part I.C.

220. *See* Krieger et al., *supra* note 94, at 638 (suggesting that investments are divided almost evenly between novel and incremental drug candidates, with novel drugs constituting 56 percent and 47 percent of big and small firms' R&D portfolios, respectively).

221. U.S. CONST. art. I, § 8, cl. 8.

222. *See* GLOBERMAN & LYBECKER, *supra* note 3, at 23–24.

223. *See* Robert P. Merges, *Uncertainty and the Standard of Patentability*, HIGH TECH. L.J., Spring 1992, at 2 ("[R]esearch which overcomes uncertainty is precisely the sort society values, and hence rewards with a patent.").

224. *See id.*

marketplace.[225] Part II.A describes arguments that favor incentivizing incremental R&D, and Part II.B describes arguments that favor limiting patent protection of incremental R&D.

A. The Law Should Incentivize Incremental R&D

Part II.A provides an inexhaustive list of reasons patent law should promote, not discourage, R&D of derivative drugs and biologics. Part II.A.1 describes how these advancements are often necessary. Part II.A.2 examines how academic research, which provides the foundation for applied industry innovation, is increasingly incremental. Lastly, Part II.A.3 clarifies that the all R&D is unpredictable, and even incremental steps can turn into breakthrough products.

1. Existing Drug Treatments Must Be Improved Through Scientific Research

Improvements to existing drugs benefit the public by advancing medical treatments,[226] as developing new drugs and biologics often requires improvements.[227] Incremental research has long been considered integral to pharmacology,[228] the study of how drugs act on bodily systems.[229] New drugs and biologics often require improvements to increase their efficacy, safety, and tolerability.[230] For example, companies improve drugs and biologics to limit side effects that make it difficult for people, especially vulnerable groups, to strictly adhere to drug regimens.[231] Drugs also vary in how often they need administration: biologics, such as vaccines, can typically be administered less often than routine medications, but they are also expensive to produce and costly to consumers.[232] By altering such parameters, companies can create pools of alternatives for prescribers to create individualized treatment plans that satisfy their patients' needs.[233] Although product value is often measured by how effective the drug is at treating illness, improvements are also needed to ensure that drugs can access wide markets, which requires stability and long shelf life.[234]

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225. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 19, at 5; *see also* Opinion, *Save America's Patent System*, N.Y. TIMES (Apr. 16, 2022), https://www.nytimes.com/2022/04/16/opinion/patents-reform-drug-prices.html [https://perma.cc/5RKD-429V].

226. *See* GLOBERMAN & LYBECKER, *supra* note 3, at 24.

227. *Id.* at 28.

228. *See* Aronson & Green, *supra* note 46, at 2116–17.

229. *See* NESTLER ET AL., *supra* note 25, at xiii.

230. *See* GLOBERMAN & LYBECKER, *supra* note 3, at 28 ("The first-in-class drug is rarely best-in-class.").

231. *See* Eyenovia Inc. v. Sydnexis, Inc., No. IPR2022-00384, at 48 (P.T.A.B. July 13, 2023) (recognizing the relationship between the concentration of an ingredient and poor patient compliance as motivation for a PHOSITA to combine prior art references).

232. *See supra* Part I.A.1.

233. *See* GLOBERMAN & LYBECKER, *supra* note 3, at 26–27.

234. David Gelles, *How to Ship a Vaccine at –80°C, and Other Obstacles in the Covid Fight*, N.Y. TIMES (Sept. 19, 2020), https://www.nytimes.com/2020/09/18/business/coronavirus-covid-vaccine-cold-frozen-logistics.html [https://perma.cc/3C2S-QY52] (describing that

Even minor changes to a drug can alter its effects.[235] For example, the addition of a single functional group, only two atoms, to the drug daunorubicin widely expanded its use. Although daunorubicin is only used to treat leukemia, doxorubicin can be used to treat a variety of cancerous tumors, including breast, bladder, skin, and ovarian cancers, to name a few.[236] Many underestimate the extent to which such minor changes can vary important properties of the product.[237] Pharmacologists, in recognition of the value of incremental innovation, typically experiment with existing drugs such that virtually all new drugs share structural similarities with existing ones.[238] Moreover, existing drugs can have radically expanded use even with no structural changes at all.[239] For example, thalidomide was found to cause birth defects when prescribed as an antiemetic during pregnancy; later, researchers discovered a new purpose for thalidomide treating certain types of cancers, including multiple myeloma.[240] Small, nonstructural changes to thalidomide created Revlimid®, a blockbuster cancer drug with greater efficacy and less toxicity.[241] "[T]he most fruitful basis for the discovery of a new drug is to start with an old drug . . . ."[242]

2. Incremental Innovation Drives Most Scientific Research Today

Industry R&D derives innovation from existing academic research.[243] "Scientific breakthroughs often build on earlier research efforts," including failures and the unpatentable exploratory work of "basic" scientists.[244] For example, basic scientists found a hormone that increases insulin production

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one of the early struggles in getting the COVID-19 vaccine to rural areas was the lack of an expensive minus eighty-degree freezer).

235. Fabrizio Giordanetto, Jonas Boström & Christian Tyrchan, *Follow-On Drugs: How Far Should Chemists Look?*, 16 DRUG DISCOVERY TODAY 722, 730 (2011) (noting that "despite such a minor change, there are considerable differences in clinical use" between two drugs).

236. *See id*; *see also Comparing Daunorubicin vs Doxorubicin*, DRUGS.COM, https://www.drugs.com/compare/daunorubicin-vs-doxorubicin [https://perma.cc/4R7X-56G7] (last visited Feb. 9, 2024).

237. *See id.*

238. *See* Krieger et al., *supra* note 94, at 646.

239. *See generally* Chong & Sullivan, *supra* note 99.

240. *See* Melchert & List, *supra* note 39, at 1490.

241. *See id.* at 1492.

242. *See* Giordanetto et al., *supra* note 235, at 731 (quoting an adage by Sir James Black). However, some research suggests that disruptive R&D has greater potential than incremental R&D to create "blockbuster" products, such as Humira®. *See* Alexander Schuhmacher, Markus Hinder, Nikolaj Boger, Dominik Hartl & Oliver Gassmann, *The Significance of Blockbusters in the Pharmaceutical Industry*, 22 NATURE REVS. DRUG DISCOVERY 177, 177 (2023). "Blockbusters" generally refer to compounds with a total annual revenue of more than one billion dollars; typically, they are the product of "high-risk" R&D of new compounds. *See id.*

243. *See generally* JP Hughes, S Rees, SB Kalindjian & KL Philpott, *Principles of Early Drug Discovery*, 162 BRIT. J. PHARMACOLOGY 1239 (2011).

244. Alexander P. Frankel, Joshua L. Krieger, Danielle Li & Dimitris Papanikolaou, *Evaluation and Learning in R&D Investment* 1 (Nat'l Bureau of Econ. Rsch., Working Paper No. 23-074, 2023), https://www.hbs.edu/ris/Publication%20Files/23-074_6d123e8a-00fd-4cd8-852e-dceab149244d.pdf.

after a meal.[245] Applied scientists within the pharmaceutical and biotechnology industries developed a compound that mimicked that hormone[246] and an injectable formulation[247] that could be used to promote weight loss, marketing it as Ozempic®.[248]

Sometimes, basic and applied scientists are one and the same.[249] Academic researchers take their work off campus and form university-licensed startups that allow both the university and the researchers to commercialize their products.[250] Industry researchers also start their careers as academics because many industry positions require graduate degrees in relevant fields.[251] Often, pharmaceutical and biotechnology companies outsource work to academic institutions to lower R&D costs.[252] Nearly all corporate publications include academic coauthors.[253] Patents are often the products of this type of beneficial exchange of scientific knowledge between academia and industry.[254]

Industry improvements also further scientific knowledge.[255] In developing a novel drug, researchers learn about its "efficacy against disease, toxicity at different levels of dosing, unintended and 'off target' benefits and side effects, interactions with other drugs, and differences in drug metabolism across patient[s]."[256] This information creates "knowledge spillovers," exposing new avenues of research.[257] Researchers also learn from failures and successfully improve many drugs that initially fail to obtain FDA approval.[258] These improvements typically occur internally because failures are rarely published; the original manufacturers have superior knowledge about a product's drawbacks.[259] Instead of limiting incremental

245. *See* Svetlana Mojsov, Gordon C. Weir & Joel F. Habener, *Insulinotropin: Glucagon-Like Peptide I (7-37) Co-encoded in the Glucagon Gene Is a Potent Stimulator of Insulin Release in the Perfused Rat Pancreas*, 79 J. CLINICAL INVESTIGATION 616, 617 (1987).

246. U.S. Patent No. 8,129,343 B2 (filed Mar. 20, 2006).

247. U.S. Patent No. 8,114,833 B2 (filed May 17, 2006).

248. NOVO NORDISK A/S, OZEMPIC® (SEMAGLUTIDE) INJECTION: PACKAGE INSERT (2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209637s003lbl.pdf.

249. *See* Paul C. Godfrey, Gove N. Allen & David Benson, *The Biotech Living and the Walking Dead*, 38 NATURE BIOTECHNOLOGY 132, 135 (2020).

250. *See id.*

251. *See* Alexander J. Spicer, Pierre-Albert Colcomb & Ann Kraft, *Mind the Gap: Closing the Growing Chasm Between Academia and Industry*, 40 NATURE BIOTECHNOLOGY 1693, 1694 (2022).

252. *See The Shifting Corporate–Academic Relationship in Pictures*, NATURE INDEX (Dec. 11, 2017), https://www.nature.com/nature-index/news/the-shifting-corporate-academic-relationship-in-pictures [https://perma.cc/5L3S-PGTN].

253. *See id.*

254. *See* Jing-Yuan Chiou, Laura Magazzini, Fabio Pammolli & Masimo Riccaboni, *Learning from Successes and Failures in Pharmaceutical R&D*, 26 J. EVOLUTIONARY ECON. 271, 273 (2016).

255. *See* GLOBERMAN & LYBECKER, *supra* note 3, at 24.

256. Frankel et al., *supra* note 244, at 6.

257. *Id.*

258. *See* Chiou et al., *supra* note 254, at 287–88.

259. *See id.*

improvements, some scholars want patent law to promote communication of failures, thereby facilitating more collaborative improvements.[260]

Authorship data suggests that the collaborative relationship between academia and industry is strengthening over time, indicating that trends in academic sciences increasingly drive industry R&D.[261] However, disruptive research has received decreased attention within the broader scientific community.[262] One reason for the change is that modern scientists "face a higher burden of knowledge"[263]—as more scientific work is published, it becomes harder for scientists to differentiate their work from existing knowledge.[264] The number of publications has grown exponentially over the last several decades; the volume doubles approximately every twenty-four years.[265] Just as companies must demonstrate the novelty and nonobviousness of their inventions to obtain patents, basic scientists must meet similar criteria to publish in high-impact journals.[266] The task of standing apart from the crowd grows more difficult with the expansion of scientific knowledge for researchers in all scientific disciplines, not just the crowded field of pharmaceutical sciences.[267]

To compensate for the burden of knowledge, scientists rely on narrower pools of prior research to inform their own research.[268] Basic scientists are moving into narrower specialties, where there is less potential of being preempted by the simultaneous discoveries of others.[269] Because it takes more training to establish such a specialty, the age at which researchers publish their first independent papers is increasing.[270] Scientists form tight-knit groups—essentially families—that self-cite and collectively promote their work.[271] They are also increasingly reliant on teamwork.[272]

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260. *See id.* (summarizing alternative schemes proposed in the field to enhance knowledge transmission).

261. *See id.*

262. *See* Michael Park, Erin Leahey & Russell J. Funk, *Papers and Patents Are Becoming Less Disruptive over Time*, 613 NATURE 138, 140 (2023).

263. *Id.* at 145. *See generally* Benjamin F. Jones, *The Burden of Knowledge and the 'Death of the Renaissance Man': Is Innovation Getting Harder?* (Nat'l Bureau of Econ. Rsch., Working Paper No. 11360, 2005), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=727140 [https://perma.cc/WBQ8-6QKE].

264. *See* Jones, *supra* note 263, at 2–3 ("Innovators also seek to avoid crowding: other things equal, the greater the density of innovators in a particular area of knowledge, the less expected income each will earn.").

265. *See* Lutz Bornmann & Rüdiger Mutz, *Growth Rates of Modern Science: A Bibliometric Analysis Based on the Number of Publications and Cited References*, 66 J. ASS'N FOR INFO. SCI. & TECH. 2215, 2217 (2015).

266. *See* Ferric Fang & Arturo Casadevall, *Competitive Science: Is Competition Ruining Science?*, 83 INFECTION & IMMUNITY 1229, 1229 (2015).

267. *See* Park et al., *supra* note 262, at 140.

268. *See id.*

269. *See id.*; *see also* Erin Leahey, *Not by Productivity Alone: How Visibility and Specialization Contribute to Academic Earnings*, 72 AM. SOCIO. REV. 533, 534 (2007).

270. *See* Sascha Schweitzer & Jan Brendel, *A Burden of Knowledge Creation in Academic Research: Evidence from Publication Data*, 28 INDUS. & INNOVATION 283, 293 (2021).

271. *See* Park et al., *supra* note 262, at 142.

272. *See* Bornmann & Mutz, *supra* note 265, at 2217; *see also* Schweitzer & Brendel, *supra* note 270, at 293.

Industry reflects this development in academia: as scientists collaborate in teams more, individual R&D scientists are obtaining fewer patents.[273] Therefore, increased incentives for disruptive research may not shift R&D priorities because there may be a "fixed 'carrying capacity' for highly disruptive science and technology."[274]

3. Incremental Research Works Because Improvements Are Unpredictable

The academic trend toward incremental research is the subject of significant discussion.[275] However, the increased attention on incremental R&D has not necessarily hurt scientific progress.[276] Firstly, disruptive research has not actually declined, as measured by the sheer number of disruptive papers and patents.[277] More studies are being published, and incremental research is occupying a progressively larger percentage of papers and patents.[278] Although researchers are specializing more, there are also more researchers than ever.[279] Teamwork within large groups, such as big pharmaceutical companies, may generate fewer novel ideas, but flexible relationships with academic institutions and small start-up companies facilitate innovation.[280] Within industry, smaller companies with less to lose are more likely to test disruptive theories,[281] and big companies rely heavily on licensing and acquisition.[282]

Secondly, incremental research might be a requirement for disruptive research, because whether an improvement is incremental or disruptive is almost impossible to predict.[283] One study examining the experiences of molecular biologists found that over half of their results were unexpected.[284] Sometimes, the biologist would make small methodological tweaks and rerun the experiment.[285] Other times, the results disrupted their understanding of the science and led to major changes in theory that required additional

273. *See* Jones, *supra* note 263, at 27.
274. Park et al., *supra* note 262, at 143.
275. *See generally* Kozlov, *supra* note 218.
276. *Id.* at 225 ("Disruptiveness is not inherently good, and incremental science is not necessarily bad . . . . The first direct observation of gravitational waves, for example, was both revolutionary and the product of incremental science . . . .").
277. *See id.*
278. *See id.*; *see also* Bornmann & Mutz, *supra* note 265, at 2217.
279. *See* JEREMY J. BAUMBERG, THE SECRET LIFE OF SCIENCE: HOW IT REALLY WORKS AND WHY IT REALLY MATTERS 22 (2018).
280. *See* Lingfei Wu, Dashun Wang & James A. Evans, *Large Teams Develop and Small Teams Disrupt Science and Technology*, 566 NATURE 378, 378 (2019).
281. *See id.*
282. *See* Schuhmacher et al., *supra* note 90, at 781.
283. *See* Kevin Dunbar & Jonathan Fugelsang, *Causal Thinking in Science: How Scientists and Students Interpret the Unexpected*, *in* SCIENTIFIC & TECHNOLOGICAL THINKING 57, 64 (Michael E. Gorman, Ryan D. Tweney, David C. Gooding & Alexandra P. Kincannon eds., 2004).
284. *See id.*
285. *See id.*

studies.[286] Researchers often incidentally learn more from their experiments than they anticipated.[287] These "off-target" effects can be serendipitous, teaching the skilled researcher far more than they intended to learn at the outset.[288]

These observations cannot be ignored in the field of pharmacology, which is a particularly unpredictable science.[289] Even result-effective variables can be difficult to control in the pharmaceutical sciences.[290] Drugs and biologics often show promise in preclinical testing but fail clinical trials.[291] Despite the increase in scientific research, the number of FDA-approved treatments each year remains low.[292] The FDA requires three phases of clinical trials of increasing size, duration, and complexity.[293] Most products fall out of development after failing the second phase for lack of sufficient proof of efficacy and safety.[294] Even after scientists collect data on anticipated adverse drug reactions, drugs can have life-threatening "idiosyncratic drug reaction[s]."[295] These reactions are nearly impossible to predict and can be related to the product's chemical characteristics or patients' unique immune responses, such as allergic reactions.[296]

Experimentation with biologics is even harder to properly control and predict than drug R&D.[297] Because biologics are isolated from living things, researchers have less control over their developmental conditions and less insight into their microscopic interactions.[298] Biologics are being deployed to treat previously unmet medical needs, often qualifying for "orphan

286. *See id.*

287. *See* Gabrielle M. Christenhusz, Koenraad Devriendt & Kris Dierickx, *Secondary Variants—in Defense of a More Fitting Term in the Incidental Findings Debate*, 21 EUR. J. HUM. GENETICS 1331, 1331 (2013) (explaining that "new genetic sequencing technologies, which can also 'see' more than the particular aim of a particular study, are ripe for an explosion of incidental findings").

288. *Id.* at 1332.

289. *See supra* Part I.A.1.

290. *See* Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1379 (Fed. Cir. 2006) (finding no clear error in the lower court's determination that "salt formation was an unpredictable exercise").

291. *See Step 3: Clinical Research*, *supra* note 84.

292. *See supra* Part I.A.3.

293. 21 C.F.R. § 312 (2024); *see also Step 3: Clinical Research*, *supra* note 84.

294. *Probability of Success for New Drugs in the U.S. by Development Phase Between 2011 and 2020, by Drug Classification*, STATISTA (Feb. 2021), https://www.statista.com/statistics/597850/drug-development-phases-probability-of-success-by-drug-classification-modality/ [https://perma.cc/REH9-ABDT].

295. Jack Uetrecht & Dean J. Naisbitt, *Idiosyncratic Adverse Drug Reactions: Current Concepts*, 65 PHARMACOLOGICAL REV. 779, 780 (2013).

296. *See id.*

297. *See supra* Part I.A.1.

298. *See* Mark Trusheim, Murray L. Aitken & Ernst R. Berndt, *Characterizing Markets for Biopharmaceutical Innovations: Do Biologics Differ from Small Molecules?* 1 (Nat'l Bureau of Econ. Rsch., Working Paper No. 16014, 2010); Dranove et al., *supra* note 16, at 4 ("[B]y the nature of their science, [biologics] are not even simple variations of each other—i.e. one cannot easily create a new biologic through a simple manipulation of an existing one.").

drug"[299] status and earning priority FDA review that fast-tracks their access to the market.[300] Although incremental R&D for both drugs and biologics is characterized by unpredictability,[301] these problems are exacerbated for biologics.[302]

The Federal Circuit recognizes the heightened unpredictability of biologics R&D.[303] In *ModernaTx, Inc. v. Arbutus Biopharma Corp.*,[304] the Federal Circuit found that Arbutus, the patentee, did not rely on routine optimization given the complexity of the interacting variables.[305] Specifically, Arbutus modified multiple components within the lipid bilayers of serum-stable nucleic acid-lipid particles (SNALPs).[306] Even if the phospholipid range was a result-effective variable, it was only one of several interdependent variables, any one of which could have hindered SNALP stability.[307] "Evidence that the components 'interacted in an unpredictable or unexpected way could render the combination nonobvious.'"[308] The Federal Circuit therefore considered how a PHOSITA would view the predictability of combining result-effective variables in order to determine routine optimization.[309] Therefore, in contrast to the holding in *Applied Materials*, the combination of multiple result-effective variables may suggest nonobviousness in biologics R&D. The PTAB has made similar findings within the context of these unpredictable arts.[310]

B. Incremental R&D Does Not Need Protection

Part II.B provides an inexhaustive list of reasons why patent protection should not extend to derivative products. Part II.B.1 suggests that the unpredictability of incremental research does not undermine its obviousness. Part II.B.2 describes how the USPTO is overburdened, leading to lower quality patents. Finally, Part II.B.3 describes how patents on incremental R&D can be abused to extend monopolies on life-saving drugs and biologics.

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299. Pharm. Rsch. & Mfrs. of Am. v. U.S. Dep't of Health & Hum. Servs., 138 F. Supp. 3d 31, 33 (D.D.C. 2015) ("Orphan drugs are so-named because, absent the . . . incentives Congress has provided to pharmaceutical manufacturers for the development of such drugs, efforts to invest, research, and otherwise manufacture those drugs would likely be abandoned.").

300. *See Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, *supra* note 95; *see also* Dranove et al., *supra* note 16, at 11.

301. *See* Tostmann, *supra* note 13, at 364.

302. *See supra* Part I.A.1.

303. *See* ModernaTx, Inc. v. Arbutus Biopharma Corp., 18 F.4th 1364, 1375 (Fed. Cir. 2021).

304. 18 F.4th 1364 (Fed. Cir. 2021).

305. *See id.* at 1375.

306. *See id.* at 1367.

307. *See id.* at 1374–75.

308. *Id.* at 1375 (quoting *In re* Applied Materials, Inc., 692 F.3d 1289, 1298 (Fed. Cir. 2012)).

309. *See id.*

310. *See* Twinstrand Biosciences v. Guardant Health, No. IPR2022-01116, at 16 (P.T.A.B. Dec. 30, 2022) (refusing to identify a variable as "a simple result-effective variable that can be determined by routine optimization" because it was one of a number of variables that could have controlled the results in developing of a genetic sequencing probe).

1. Incremental R&D Can Be Both Unpredictable and Obvious to Try

In asking whether an invention was obvious to try, the inventor's expected result has limited relevance.[311] The problem ultimately solved by the invention does not need to be what the scientist intended to solve.[312] For example, in *Alcon Research v. Apotex*,[313] Alcon patented a method of treating allergic eye disease with eye drops that stabilize mast-cell activity.[314] Apotex asserted that the patent was invalid for obviousness because the eye drops were already known to treat allergies by limiting antihistamine release.[315] The Federal Circuit agreed that antihistamine effects motivated a PHOSITA to experiment with the eye drops.[316] It was irrelevant to the court that the novel mast-cell effect had actually motivated the inventor.[317]

Although there must be a "reasonable expectation of success,"[318] some unpredictability regarding the result does not mean that the experiment itself was not obvious to try.[319] "Absolute predictability . . . is not required."[320] As with the predictable sciences, variables can be obvious to try if the prior art "identifies the *important parameters*."[321] For example, the inventors in *Valeant Pharmaceuticals International v. Mylan Pharmaceuticals*[322] combined multiple variables in their development of the drug methylnaltrexone, including buffering, isotonicity, chelating agents, container closure systems, and preservatives.[323] The patent claimed a preparation of the drug that was stable for two years at a "pH between about 3.0 and about 4.0."[324] A generic manufacturer asserted that the invention was obvious because "structurally and functionally similar" drugs were known to be stable at the claimed pH.[325] Although admitting that the prior art provided a PHOSITA with "good places to start looking" for solutions, the lower court granted summary judgment to the patentee in light of the

311. Brunswick Corp. v. Volvo Penta of the Ams., No. IPR2020-01512, at 19 (P.T.A.B. Mar. 3, 2022) (finding that "the *actual* reason that [the patentee] modified *its own* prior device(s) . . . does not undermine an adequately supported, *yet different*, reason that [a PHOSITA] would have modified the relied-upon prior art references").

312. *See id.*

313. 687 F.3d 1362 (Fed. Cir. 2012).

314. *See id.* at 1363.

315. *See id.* at 1366.

316. *See id.* at 1368 ("We have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same motivation that the patentee had.").

317. *See id.*

318. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1367 (Fed. Cir. 2007).

319. *Id.* at 1366 ("Although we recognize some degree of unpredictability of salt formation, the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious." (citation omitted)).

320. Valeant Pharms. Int'l Inc. v. Mylan Pharms. Inc., 955 F.3d 25, 34 (Fed. Cir. 2020).

321. R.J. Reynolds Vapor Co. v. Philip Morris Prods. S.A., No. IPR2021-00585, at 57 (P.T.A.B. Sept. 8, 2022).

322. *Valeant*, 955 F.3d 25.

323. *See id.*

324. *Id.* at 27.

325. *Id.* at 30 (referring to naloxone and naltrexone).

challenging combination of variables with which the inventors could have experimented.[326] The Federal Circuit reversed, noting that "there is no requirement that for a variable to be obvious to try, it must be the first variable a person of skill would alter."[327] The extensive funding, time, and effort expended for R&D does not indicate that it did not rely on routine optimization.[328]

2. The USPTO Is Already Overburdened

USPTO personnel examine more than half a million patents each year,[329] and each patent receives about nineteen hours of review before a decision is made.[330] In this time, the examiner must survey the prior art; conduct inquiries of utility, novelty, and nonobviousness; and write a response.[331] Weak applications add to the burden on personnel and are often approved by personnel facing time limitations.[332] Analyzing over one million applications, Professors Michael Frakes and Melissa Wasserman found that less time allocated to patent examination meant less robust investigations of prior art.[333] As a result, these personnel were less likely to reject patent applications on the grounds of obviousness.[334] The patents granted were of below average value, meaning they were less likely to be renewed and were cited less in subsequent patents.[335] In their recent proposal, the nonprofit group Initiative for Medicines, Access, and Knowledge (I-MAK) proposed setting up an independent panel of "pharmaceutical scientists, clinical trial and efficacy data experts, physicians, public interest patent and intellectual property attorneys, academics, and patients affected by the drug in question" to facilitate patent examination.[336]

The burden of weak patents on the USPTO is further exacerbated by the policy that patent applicants can restart the application process; effectively, the USPTO cannot bar a past applicant from filing a repeat application.[337]

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326. Valeant Pharms. Int'l, Inc. v. Mylan Pharms., Inc., No. CV-15-8180, 2018 WL 2023537, at *10 (D.N.J. May 1, 2018), *rev'd and remanded*, 955 F.3d 25 (Fed. Cir. 2020).

327. *Valeant*, 955 F.3d at 34.

328. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1367 (Fed. Cir. 2007).

329. *See* U.S. PAT. & TRADEMARK OFF., U.S. PATENT STATISTICS REPORT 1 (2021), https://www.uspto.gov/web/offices/ac/ido/oeip/taf/us_stat.htm [https://perma.cc/22TX-HUK4].

330. Michael D. Frakes & Melissa F. Wasserman, *Is the Time Allocated to Review Patent Applications Inducing Examiners to Grant Invalid Patents?: Evidence from Micro-level Application Data* 8 (Nat'l Bureau of Econ. Rsch., Working Paper No. 20337, 2014), https://www.nber.org/system/files/working_papers/w20337/w20337.pdf [https://perma.cc/4SCG-LXXP].

331. *See id.*

332. *See id.* at 39.

333. *See id.*

334. *See id.*

335. *See id.* at 14.

336. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 19, at 3.

337. MICHAEL D. FRAKES & MELISSA F. WASSERMAN, HAMILTON PROJECT & BROOKINGS INST., DECREASING THE PATENT OFFICE'S INCENTIVES TO GRANT INVALID PATENTS 16 (2017), https://www.brookings.edu/wp-content/uploads/2017/12/es_121317_decreasing_patent_office_incentives_grant_invalid_patents.pdf [https://perma.cc/XQV9-5YAD]. Applicants can

Professors Frakes and Wasserman suggest limiting repeat applications to reduce the burden on the USPTO.[338]

3. Increased Risk of Foul Play and Exploitation of Patentable Improvements

Patentees can exclude others from the profits of their inventions and set high prices for licensees and consumers.[339] Although the Sherman Antitrust Act [340] prohibits anticompetitive conduct, patents give companies an exception to that policy but only for a limited period of time.[341] Patents that are not invalidated eventually hit a "patent cliff" when the patent owner's monopoly expires and competitors flood the market.[342] For example, when the patent on Pfizer's erectile dysfunction drug Viagra expired in 2017, the company's sales of the drug nearly halved within a year and continued to decline in subsequent years.[343]

Patentees may violate the terms of the antitrust exception when they take unreasonable measures to extend the duration of their rights.[344] Through a process disparagingly known as "evergreening," patent owners extend their patents' life cycles by making trivial changes to their products sufficient to withstand patent examination.[345] One means of doing so is by obtaining as many patents as possible, each acting as a shield to protect the primary patent. [346] This patent portfolio is commonly referred to as a "patent thicket."[347] Many of the patents in the portfolio protect inventions, such as a dose regimen for the drug, that may not be different enough from the pioneer patent to be independently patentable.[348] For example, Humira® was

apply for continued examination after the initial application has been rejected. *See id.* In 2016, 40 percent of applications filed were repeat applications. *Id.* at 10.

338. *See id.* at 14.

339. *See* SCM Corp. v. Xerox Corp., 645 F.2d 1195, 1203 (2d Cir. 1981) ("[P]atent laws reward the inventor with a temporary monopoly that insulates him from competitive exploitation of his patented art.").

340. 15 U.S.C. § 1.

341. *See* Mark S. Levy, *Big Pharma Monopoly: Why Consumers Keep Landing on "Park Place" and How the Game Is Rigged*, 66 AM. U. L. REV. 247, 256–57 (2016).

342. *See id.* at 276–77; *see also In re* Suboxone (Buprenorphine Hydrochloride & Naloxone) Antitrust Litig., 622 F. Supp. 3d 22, 55 (E.D. Pa. 2022).

343. *Worldwide Revenue of Pfizer's Viagra from 2003 to 2019 (in Million U.S. Dollars)*, STATISTA, https://www.statista.com/statistics/264827/pfizers-worldwide-viagra-revenue-since-2003/ [https://perma.cc/N9FT-SVJ9] (last visited Feb. 9, 2024).

344. *See* Fed. Trade Comm'n v. Actavis, Inc., 570 U.S. 136, 150 (2013). For example, companies cannot pay competitors to withhold their patent challenges. *Id.*

345. *See* Furrow, *supra* note 98, at 276; *see also* MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES 72 (2005). Dr. Marcia Angell, the first female Editor-in-Chief of the New England Journal of Medicine, likened modern pharmaceutical patents to leftovers from dinner—companies can profit from pioneer patents well after they should have expired. *Id.*

346. Rachel Goode & Bernard Chao, *Biological Patent Thickets and Delayed Access to Biosimilar, an American Problem*, J.L. & BIOSCIENCES, July–Dec. 2022, at 1, 2.

347. *Id.*

348. *See id.* at 19.

protected by over 130 patents.[349] One study found that over 75 percent of the Humira® patents were "non-patentably distinct" from the rest of their patent family.[350]

Incremental R&D is not inherently anticompetitive, and marketing a minor improvement does not violate antitrust law.[351] However, the marketing of derivative products in conjunction with anticompetitive conduct, such as misrepresenting aspects of those products to coerce prescribers, may have anticompetitive effects.[352] Circumstances surrounding marketing, such as an impending patent cliff, may be relevant to the analysis.[353] If plaintiffs can show anticompetitive effects,[354] the burden shifts to defendants to offer "legitimate business reasons" for their decision-making.[355] Humira® purchasers sued AbbVie for violating antitrust laws, but their complaint was dismissed because it was too speculative.[356] Although the difficulty of showing anticompetitive effects limits the use of antitrust law, reforms can instead target the underlying sources of patent thickets, including overbroad claims and OTDP.[357]

Patent thickets form when companies broadly claim, for example, various indications for which the product may have use, and later file separate, secondary applications claiming more detailed methods of using the product for these indications.[358] The Supreme Court in *Amgen Inc. v. Sanofi*[359] restrained industry use of overbroad claims in product patents.[360] Some proposed reforms suggest a higher standard of obviousness be applied to these secondary patents,[361] but the Court in *Amgen* criticized the primary overbroad claims.[362] Amgen had developed a breakthrough biologic,

349. *See* Rebecca Robbins, *How a Drug Company Made $114 Billion by Gaming the U.S. Patent System*, N.Y. TIMES (Jan. 28, 2023), https://www.nytimes.com/2023/01/28/business/humira-abbvie-monopoly.html [https://perma.cc/G8TV-KP4T].

350. Goode & Chao, *supra* note 346, at 19. These include families that protect the basic product, the formulation, and primary and secondary indications, among others. *Id.* at 18.

351. *See* Mylan Pharms., Inc. v. Warner Chilcott Pub. Co., No. CV-12-3824, 2015 WL 1736957, at *16 (E.D. Pa. Apr. 16, 2015), *aff'd*, 838 F.3d 421 (3d Cir. 2016) (taking care not to disincentivize innovation, the district court noted that "costly and uncertain litigation every time a company reformulates a brand-name drug would likely increase costs and discourage manufacturers").

352. *See In re* Suboxone (Buprenorphine Hydrochloride & Naloxone) Antitrust Litig., 622 F. Supp. 3d 22, 54 (E.D. Pa. 2022).

353. *See id.*

354. *See id.* at 59 ("Mere harm to competitors will not suffice; rather the alleged exclusionary acts must harm the competitive process and must actually have the requisite anticompetitive effect.").

355. *Mylan*, 2015 WL 1736957, at *5.

356. *See In re* Humira (Adalimumab) Antitrust Litig., 465 F. Supp. 3d 811, 843 (N.D. Ill. 2020), *aff'd sub nom.* Mayor of Balt. v. AbbVie Inc., 42 F.4th 709 (7th Cir. 2022).

357. *See supra* Part I.B.

358. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 19, at 8.

359. 598 U.S. 594 (2023).

360. *Id.* at 610.

361. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 19, at 5.

362. *See Amgen*, 598 U.S. at 613; *see also supra* Part I.A.2 (discussing the enablement standard of 35 U.S.C. § 112, which requires that a patent fully enable a PHOSITA to copy the invention).

marketed as Repatha, that lowers blood levels of harmful low-density lipoprotein cholesterol.[363] It contains an antibody that targets a specific receptor that breaks down fatty acids.[364] A million other antibodies might target this receptor, in part because "aspects of antibody science remain unpredictable."[365] To find these other antibodies, a PHOSITA would have to conduct more than a "reasonable degree of experimentation" with an unknowable number of antibody options.[366] Therefore, the Court found the claims too broad to enable a PHOSITA to practice the invention.[367]

The availability of terminal disclaimers to overcome rejections based on OTDP also contributes to patent thicket formation.[368] The USPTO proposed changes to OTDP doctrine that would require companies to concede that their products are obvious and unpatentable without a terminal disclaimer.[369] Between 2022 and 2023, the USPTO solicited public commentary on their new initiatives to bolster patent integrity.[370] Although many critics, including members of Congress, support greater restrictions on OTDP,[371] industry responses have been largely negative.[372] Companies want to eliminate OTDP rejections altogether.[373] Companies resent the USPTO's discouragement of incremental yet patentable inventions,[374] but the USPTO

363. *Amgen*, 598 U.S. at 599.

364. *See id.*

365. *Id.* at 600 ("For example, scientists understand that changing even one amino acid in the sequence can alter an antibody's structure and function.").

366. *Id.* at 613.

367. *Id.* at 610 (holding that "[t]he more one claims, the more one must enable").

368. *See* Wu & Cheng, *supra* note 36, at 140; *see also supra* Part I.B.1.

369. Request for Comments on USPTO Initiatives To Ensure the Robustness and Reliability of Patent Rights, 87 Fed. Reg. 60130, 60131 (Oct. 4, 2022). Terminal disclaimers can be used to overcome OTDP rejections, but the USPTO's proposal would create a presumption that the underlying invention is unpatentable. *See* 3A DONALD S. CHISUM, CHISUM ON PATENTS § 9.04 (2023).

370. Request for Comments on USPTO Initiatives To Ensure the Robustness and Reliability of Patent Rights, 87 Fed. Reg. at 60131.

371. *See* Letter from Elizabeth Warren, U.S. Sen. & Pramila Jayapal, Member of Cong., to Honorable Kathi Vidal, Dir. of U.S. Pat. & Trademark Off. (Apr. 26, 2023); *see also supra* Part II.B.1.

372. *See, e.g.*, Comment Letter from Amgen Inc. to Honorable Kathi Vidal, Dir. of U.S. Pat. & Trademark Off. (Feb. 1, 2023), https://www.regulations.gov/comment/PTO-P-2022-0025-0114 [https://perma.cc/DP3J-7SZF]; Comment Letter from Brian H. Bazli, President, Am. Intell. Prop. L. Ass'n, to Honorable Katherine K. Vidal, Dir. of U.S. Pat. & Trademark Off. (Feb. 1, 2023), https://www.regulations.gov/comment/PTO-P-2022-0025-0109 [https://perma.cc/D43U-27QM]; Comment Letter from Henry Hadad, Senior Vice President & Deputy Gen. Couns., Bristol Myers Squibb, to Honorable Kathi Vidal, Dir. of U.S. Pat. & Trademark Off. (Feb. 1, 2023), https://www.regulations.gov/comment/PTO-P-2022-0025-0117 [https://perma.cc/R68M-UEM7].

373. *See* Comment Letter from Henry Hadad, Bristol Myers Squibb, to Honorable Kathi Vidal, *supra* note 372, at 10 (noting that, because OTDP is judicially-made doctrine, the USPTO cannot unilaterally eliminate it and should not expand it further as proposed in the request for comments).

374. *See id.* at 3.

appears to be promulgating policy in line with aforementioned judicial and congressional interests—namely, limiting patent monopolies.[375]

Congress has made similar attempts to modify patentability standards to reduce drug prices.[376] Senator Lindsey Graham proposed but never introduced the "No Combination Drug Patents Act" in 2019 that would have created a presumption of obviousness for any drug or biologic present in prior art.[377] Under that act, a patent would have been presumed obvious for claiming a dosing regimen, method of administration, method of treatment for a previously uncovered ailment, or even a new formulation.[378] To rebut that presumption, patentees would essentially need to structurally alter the active ingredient or at least demonstrate a "statistically significant" increase in drug or biologic efficacy.[379] As a whole, the proposal suggested that many pharmaceutical and biotechnology products are intrinsically obvious.[380] It assumed that companies know a product's full therapeutic potential but choose not to claim the full scope of the invention so they can later obtain a potential patent thicket.[381] Erroneously assuming that novel and incremental advancements can be reliably differentiated, the proposal subjected incremental R&D to a higher standard.[382]

Incremental innovation has proven itself valuable to pharmaceutical and biotechnological progress, yet it may also facilitate high costs of healthcare.[383] In 2021, President Joseph R. Biden noted in his Executive Order on Promoting Competition in the American Economy[384] that "too often, patent and other laws have been misused to inhibit or delay—for years

375. *See* Steve Brachmann, *Congress Adds TERM Act and No Combination Drug Patents Act to List of Drug Patent Bills Being Considered*, IPWATCHDOG (June 20, 2019, 9:15AM), https://ipwatchdog.com/2019/06/20/congress-term-act-no-combination-drug-patents-act-added-list-drug-patent-bills-considered/id=110525/ [https://perma.cc/X82A-2J4K] (noting that "lawmakers have zeroed in on the idea that many pharmaceutical patents cover little more than combinations of prior art drugs and delivery methods, with little regard for the increased therapeutic benefits of different dosage regimens or delivery mechanisms").

376. *See id.*

377. *See id.*

378. *See id.*

379. Kevin Madigan & Sean O'Connor, *"No Combination Drug Patents Act" Stalls, but Threats to Innovation Remain*, GEO. MASON U. C-IP^2 (June 27, 2019), https://cip2.gmu.edu/2019/06/27/no-combination-drug-patents-act-stalls-but-threats-to-innovation-remain/ [https://perma.cc/TBM5-XZRL].

380. *See* Christopher M. Holman, *Congress Should Decline Ill-Advised Legislative Proposals Aimed at Evergreening of Pharmaceutical Patent Protection*, 51 U. PAC. L. REV. 493, 518 (2020).

381. *Id.* at 516–17.

382. *See* Madigan & O'Connor, *supra* note 379 (arguing that incremental advancements, such as "[n]ew formulations of malaria drugs, dosing regimens and delivery systems for AIDS patients, more efficient administrations of insulin for the treatment of diabetes, and developments in the treatment of cognitive heart disease," should not be made subject to higher patentability standards than other technologies because doing so would disincentivize incremental R&D).

383. *See generally* AM. ECON. LIBERTIES PROJECT & INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, THE COSTS OF PHARMA CHEATING (2023).

384. Exec. Order No. 14036, Promoting Competition in the American Economy, 86 Fed. Reg. 36987 (July 9, 2021).

and even decades—competition from generic drugs and biosimilars, denying Americans access to lower-cost drugs."[385] Because obvious improvements shield products from competition, stricter analysis of obviousness may deprive companies of their defenses and lower drug prices.[386]

In summary, patent protection has consequences, such as higher prices, that some argue do not justify the benefits of incremental R&D; others argue that incremental R&D has immense value and should be encouraged.[387] Part III reconciles these perspectives by clarifying the nonobviousness standard as it applies to incremental improvements and recommending alternative solutions for regulating pharmaceutical and biotechnological industry activity.

III. INCREMENTAL IMPROVEMENTS TO PATENT LAW

Patents that protect drugs and biologics are particularly vulnerable to invalidation on the grounds that they were obvious to try.[388] This vulnerability is partly due to the presence of result-effective variables in pharmacological research, such as concentration, pH value, and temperature.[389] The presence of result-effective variables makes it more difficult for patentees to rebut observations of routine optimization in their R&D.[390] Because result-effective variables are identified by prior art, such as scientific literature, this issue will likely increase as scientific progress continues. As the burden of scientific knowledge increases,[391] so will the burden on patentees to rebut evidence of routine optimization. However, frequent findings of routine optimization benefit consumers in the short-term by invalidating profit-protective patents.[392]

Against this background, this Note makes three interrelated points. Part III.A argues that the long-term costs of increasing the burden of nonobviousness outweigh the short-term benefits to consumers. Accordingly, Part III.B suggests that the USPTO should settle on a narrow definition of routine optimization. Finally, Part III.C supports practical reforms that limit anticompetitive conduct while maintaining the integrity of patentability standards.

A. Patent Law Should Reflect the Value of Incremental R&D

The nonobviousness standard of patent law should reflect the realities of scientific research. Pharmaceutical and biotechnology R&D is increasingly

385. *Id.* at 36988.

386. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 19, at 3; *see also* Comment Letter from Alex Moss, Exec. Dir., Pub. Int. Pat. L. Inst. (February 1, 2023), https://www.regulations.gov/comment/PTO-P-2022-0025-0105 [https://perma.cc/9DLE-74WR].

387. *See supra* Part II.

388. *See* Lemley, *supra* note 148, at 1371.

389. *See supra* Part I.C.1.

390. *See supra* Part I.D.

391. *See supra* Part II.A.2.

392. *See supra* Part II.B.3.

incremental.[393] This reality is unlikely to see dramatic change because R&D builds on an increasingly rich background of academic progress.[394] Therefore, policies that exclusively reward disruptive research based on likely misguided notions of declining innovation[395] will be ineffective. The scientific literature contains a virtually endless pool of possible research avenues,[396] and it would be negligent to ignore those for fear that those avenues are considered obvious. This Note argues that patent law should not discourage incremental research and that standards of patentability should not be sacrificed in an effort to curb exploitative conduct.

In its efforts to incentivize disruptive research, patent law is ineffectively fighting the tide.[397] Incremental R&D will continue to expand, and efforts to control anti-consumer behaviors using patent law can hurt scientific progress by disincentivizing valuable improvements.[398] The modern application of the flexible nonobviousness standard has become less functional as a tool to motivate R&D.[399]

Both the Federal Circuit and the PTAB have demonstrated a willingness to oversimplify the pharmaceutical and biotechnological sciences.[400] When research can be distilled down to a single result-effective variable, it becomes easier for the reviewing body to find obviousness. For example, in *Valeant*, the Federal Circuit discounted the extent to which the result-effective variables might interact with each other to produce unpredictable results.[401] Although the inventor could have changed a number of variables to reach the desired stability, the court found it irrelevant whether or not pH would have been the starting point for a PHOSITA.[402] In the court's opinion, the district court was wrong to overcomplicate the research.[403] *Valeant* reflects the Federal Circuit's tendency to peel away the layers of R&D complexity to find evidence of routine optimization.

This oversimplification has trickled down to USPTO guidance regarding obviousness rejections.[404] *KSR* required patent rejections to be accompanied by explicit rationales, not just conclusory statements of obviousness, and subsequent USPTO guidance provided a number of rationales for obviousness.[405] The PTAB judges need only explicitly supply one, with or

393. *See supra* Part II.A.2.
394. *See supra* Part II.A.2.
395. *See* Kozlov, *supra* note 218, at 225 (describing that disruptive research has declined, though the authors of the study referenced actually show that only the percentage of disruptive publications out of all publications has declined, not the number of disruptive publications).
396. *See* Park et al., *supra* note 262, at 143.
397. *See supra* Part II.A.2.
398. *See supra* Part II.A.1.
399. *See supra* Part I.B.3.
400. *See supra* Part II.A.3.
401. Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc., 955 F.3d 25, 34 (Fed. Cir. 2020).
402. *Id.*
403. *Id.*
404. MPEP § 2143 (9th ed. Rev. 7, Feb. 2023).
405. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007); *see also* MPEP § 2143.

without similarly explicit supporting evidence.[406] These arbitrary rationales set by case law and the MPEP allow judges to mask subjective judgments as evidence-based findings of obviousness. Subjective judgments follow trends that are predictable in the short term but provide little guidance for companies strategizing decades of R&D. The PTAB is currently instituting inter partes review at their highest rate yet, up nearly 15 percent in less than two years.[407] Moreover, once a prima facie case has been satisfied, the PTAB is notably reluctant to examine evidence of secondary indicia, such as unexpected results.[408] Collectively, because of the flexibility awarded to courts and the PTAB, patented improvements face uncertain futures in litigation.

B. Routine Optimization Should Be Narrowly Defined

Although *KSR* did not directly speak to the routine optimization of pharmacological variables, "[c]ases following *KSR* have considered whether a given molecular modification would have been carried out as part of routine testing."[409] Prior to *KSR*, result-effective variables were relevant after the patent challenger met a prima facie case of obviousness based on optimization; the patentee could rebut by showing that the optimized variable was not result-effective.[410] Although this application of the doctrine is still relevant,[411] recent petitions for inter partes review at the PTAB suggest challengers are using the presence of result-effective variables as evidence of routine optimization.[412] *KSR* likely prompted this shift in usage.[413] As noted in the MPEP, result-effective variables motivate a PHOSITA to experiment, so, following *KSR*, they can serve as evidence that an experiment was obvious to try.[414] Assuming petitioners continue to find success with this practice, result-effective variables will likely become even more relevant to pharmaceutical and biotechnological companies facing patent litigation.

Patentees have limited, ineffectual ways of addressing the presence of result-effective variables. Patentees must either (1) clarify that the teachings of the prior art do not indicate that the variable is result-effective or (2) show that, although the variable is result-effective, the prior art does not sufficiently describe how the variable could be optimized to reach that

406. *See KSR*, 550 U.S. at 418; *see also* Thomas, *supra* note 201, at 2082 ("Under *KSR* . . . factfinders can engage in a wider, flexible inquiry and reach conclusions of obviousness without having to point to specific pieces of prior art . . . .").

407. *See* Ward & Cerulli, *supra* note 77.

408. *See* Kass, *supra* note 207.

409. Procter & Gamble Co. v. Teva Pharms. USA, Inc., 566 F.3d 989, 996 (Fed. Cir. 2009).

410. *See* MPEP § 2144.05(III)(C).

411. *See* E.I. DuPont de Nemours & Co. v. Synvina C.V., 904 F.3d 996, 1006 (Fed. Cir. 2018).

412. *See, e.g.*, Alcon Inc. v. Amo Dev., LLC, No. IPR2021-00845 (P.T.A.B. Nov. 4, 2022); R.J. Reynolds Vapor Co. v. Philip Morris Prods. S.A., No. IPR2021-00585 (P.T.A.B. Sept. 8, 2022).

413. MPEP § 2144.05(III)(C) ("[A]fter *KSR*, the presence of a known result-effective variable would be one, but not the only, motivation for a [PHOSITA] to experiment to reach another workable product or process.").

414. *See id.*

result.[415] Given how low the bar is for a variable to qualify as result-effective, the latter strategy likely holds more promise for patentees.[416] However, this route is becoming increasingly uncertain as the Federal Circuit refuses to draw hard-line rules, and the MPEP offers little guidance to personnel regarding how to interpret result-effective variables.[417] Courts and the PTAB have discretion to determine whether the prior art provided a "reasonable expectation of success" on a case-by-case basis.[418] This flexibility has benefits; for example, they can weed out deceitful attempts at innovation that are ultimately meant to grow patent thickets. However, given that these bodies may have imperfect scientific expertise in the rapidly advancing field of biologics, modest limitations could bring some stability to the routine optimization analysis.

"Obvious to try" findings are difficult to rebut using objective indicia of nonobviousness. Firstly, thoughtful consideration of unexpected results conflicts with the "obvious to try" analysis.[419] A PHOSITA's expectations of results could be deemed irrelevant if the experiment was obvious to try in the first place.[420] Secondly, indicia can be counterproductive following *KSR*. When a patentee introduces evidence of secondary indicia, including long felt need, praise, or commercial success, they are revealing gaps in the field filled by their invention that would have motivated a PHOSITA to experiment. For example, evidence of a long felt need partially satisfies the "obvious to try" inquiry by showing "design need."[421] On the other hand, unexpected results are irrelevant if the invention did not satisfy an unmet need.[422] According to the Federal Circuit, a PHOSITA would not be surprised by a solution to a problem if they did not know the problem existed in the first place.[423] Unexpected results are a hallmark of pharmacological research and have the potential to convert incremental experiments into

415. *See R.J. Reynolds Vapor*, No. IPR2021-00585 at 45.

416. *See supra* Part I.C.1.

417. *See supra* Part I.C.2; *see also* Actelion Pharms. Ltd. v. Mylan Pharms. Inc., 85 F.4th 1167, 1171 (Fed. Cir. 2023).

418. *See* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1365–69 (Fed. Cir. 2007).

419. *See* Trask, *supra* note 14, at 2644.

420. *See id.*

421. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). The Federal Circuit has demonstrated its confusion regarding the relationship between unmet need and motivation. *See* Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc., 25 F.4th 1354, 1376 (Fed. Cir. 2022) ("fail[ing] to see how, on the one hand [the flawed formulations that were used before NARCAN®] can provide a skilled artisan with the motivation to arrive at the claimed invention and, on the other hand, satisfy an unmet need in the prior art"). The court also found that the unmet need did not exist for long enough, given that the FDA released a statement in response to the opioid crisis only three years earlier. *Id.*

422. *See* Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC, 918 F.3d 928, 937 (Fed. Cir. 2019).

423. *See id.* ("[A PHOSITA] could not have been surprised that the sublingual route of administration did not result in cardiotoxic effects because the [PHOSITA] would not have been aware that other routes of administration do result in cardiotoxic effects.").

blockbuster treatments.[424] However, they have unreliable utility in rebutting obviousness, especially at the PTAB.[425]

Although a broader definition of routine optimization would ideally be adopted by both the Federal Circuit and the USPTO, this Note primarily proposes that the USPTO provide more comprehensive guidance regarding optimization of result-effective variables. As an MPEP amendment for USPTO personnel, courts would not be bound.[426] However, if increased guidance improves patent examination and PTAB review, then a more reliable standard of routine optimization would hopefully be adopted by courts in the future.

Stricter guidance regarding routine optimization can improve reliability of the patent system. Because research is fundamentally incremental, all work could qualify as routine optimization if the term is not given boundaries. This Note proposes two categories of changes to the doctrine. First, the Federal Circuit and USPTO should place a greater burden on patent challengers to show explicit disclosures in the prior art of "finite options" for optimizing result-effective variables. For example, if a prior art range is only close to, but does not overlap with, claimed ranges, it should not support a finding of obviousness. A result-effective variable should not shift the burden to the patentee in the absence of explicit overlap between the claimed and prior art ranges. Second, if multiple variables are modified to obtain the result, their combination should be nonobvious unless there is clear evidence of dependency of the variables. For example, if a scientist modified both pH and terminal methyl groups to confer greater stability, a PHOSITA should understand how pH alters the efficacy of a terminal methyl group before a prima facie case is satisfied.

1. Overlapping Ranges

Overlap between claimed and prior art ranges is difficult for patentees to rebut.[427] Currently, a claimed range is obvious if it is (1) broader than that disclosed in the prior art, (2) narrower than that disclosed in the prior art, or (3) is "very close" to or abuts that disclosed in the prior art.[428] If a challenger shows overlapping ranges, the patentee can rebut obviousness by demonstrating that the claimed range was critical.[429] However, criticality is difficult to show without data revealing how the nonoverlapping values of the disclosed range meaningfully fail.[430] In other words, criticality can only be shown if the experimenter uses routine optimization to test each of a

424. Part II.A.1.
425. Part I.D.
426. *In re* Rudy, 956 F.3d 1379, 1382 (Fed. Cir. 2020) ("[USPTO g]uidance is not, itself, the law of patent eligibility, does not carry the force of law, and is not binding in [courts'] patent eligibility analysis."); *see* cxLoyalty, Inc. v. Maritz Holdings Inc., 986 F.3d 1367, 1375 n.1 (Fed. Cir. 2021) (quoting *Rudy*, 956 F.3d at 1382.).
427. *See supra* Part I.C.2.
428. *See supra* Part I.C.2.
429. *See supra* Part I.D.
430. *See supra* Part I.D.

"finite number of identified, predictable solutions"[431] and thereby identify critical values. Criticality is consequently an easier issue to address at the patent prosecution phase when patentees describe the scope of their claims than at the litigation phase.

Because overlapping ranges can be sufficient to satisfy a prima facie case of obviousness,[432] explicit disclosure should be required. Additionally, a close or abutting range should not be sufficient to make a prima face case of obviousness. Similarly, the prior art should disclose the range of an identical compound, not a structurally or functionally similar compound. The "obvious to try" doctrine assumes that the experimenter tried values within a finite list of options.[433] However, a patent should not be rejected or invalidated if the examiner cannot define the range of values a PHOSITA would try by looking at the prior art. Although the Court in *KSR* supported the use of common sense inquiries,[434] the standard is unnecessarily uncertain in this context. Courts will never have a comprehensive explanation of what values are close enough, as the value that is close for one variable (e.g., one milligram) may not be close for another variable (e.g., pH change of one).[435] Moreover, this flexibility is a slippery slope; if a one-step deviation is close enough, then a two-step deviation is not much more.

Moreover, disclosing the range should not be enough; the prior art range should not be overbroad. The controlling doctrine should reflect that of enablement set forth in *Amgen Inc. v. Sanofi*.[436] The disclosure should be sufficient such that, in the absence of the claimed values, a PHOSITA could practice the invention using only the prior art range without "undue experimentation."[437] In other words, the prior art should fully enable the claims. If the prior art discloses a range of values with potential to produce a result, the amount of necessary experimentation to reach the effective value(s) should be reasonable. Importantly, what qualifies as undue experimentation depends on the art—unpredictable arts such as the pharmaceutical and biotechnological sciences require more information to meet the standard.[438] The recognition that unpredictability undermines the reasonableness of experimentation that is already present in the enablement standard should extend to the obviousness standard.

2. Multiple Variables

Federal Circuit precedent suggests that optimizing a combination of multiple result-effective variables can still be obvious, but the relevant inquiry is unclear.[439] A prima facie case of obviousness should require

431. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 402 (2007).
432. *See supra* Part I.C.2.
433. *KSR*, 550 U.S. at 421.
434. *See id.* at 403.
435. *See supra* Part I.C.2.
436. 598 U.S. 594 (2023); *see supra* Part II.B.
437. MPEP § 2164.06 (9th ed. Rev. 7, Feb. 2023).
438. *See* MPEP § 2164.06; *see also supra* Part I.A.2.
439. *See supra* Part I.C.2.

showing that (1) each variable is result-effective and (2) how the variables interact with each other is well established in prior art and would therefore be understood by a PHOSITA. The unpredictability of the art should be relevant to whether variables can be combined with a reasonable expectation of success.

In the mechanical sciences, the analysis is relatively straightforward. In *Applied Materials*, the experimenter improved a polishing pad used to flatten the surface of substrates used to form integrated circuits.[440] The groove depth and width on a polishing pad would have respectively influenced polishing capacity.[441] More importantly, the relationship between depth and width was predictable.[442] This analysis, however, is overtaxing within the pharmaceutical and biotechnological sciences given the inevitable interdependence of variables.[443] It is difficult to alter one variable without unexpectedly altering another, and the careful balance of interdependent factors requires extensive training and expensive clinical trials.[444] Although some courts, including the Federal Circuit in *ModernaTx*,[445] recognize the uniqueness of the unpredictable sciences, the standard remains unnecessarily flexible.

C. Reform Does Not Need to Disadvantage Incremental R&D

Consumers deserve protection against misusers of their inelastic demand for life-saving products, but reform measures should not raise the nonobviousness standard. Proposals to raise the nonobviousness standard ignore the benefits of incremental innovation and "throw the baby out with the bathwater."[446] Changes to patentability standards should not be used to curb evergreening behavior when alternatives, such as increased antitrust and price regulations, are available.

USPTO procedural reforms can increase the efficiency and reliability of the patent system.[447] Increased USPTO personnel and time allotments for patent examination can improve patent quality.[448] A specialized expert cannot reliably conduct a thorough review in under twenty-four hours.[449] Although patent examiners are already budgeted insufficient time for review, the continued growth of the pharmaceutical and biotechnological sciences

440. *See In re* Applied Materials, Inc., 692 F.3d 1289, 1298 (Fed. Cir. 2012).
441. *See id.* at 1296.
442. *See id.* at 1298 ("Evidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious, but Applied failed to show anything unpredictable or unexpected in the interaction of the variables." (citation omitted)).
443. *See supra* Part II.A.3.
444. *See supra* Part II.A.3.
445. ModernaTx, Inc. v. Arbutus Biopharma Corp., 18 F.4th 1364 (Fed. Cir. 2021).
446. *See* Wu & Cheng, *supra* note 36, at 165 ("We should not sacrifice the benefits provided by these laws for the sole reason of ridding patent thickets or its undesirable effects. However, to achieve a sweet spot where innovation is rewarding but at an acceptable cost of public interest is anything but simple.").
447. *See supra* Part II.B.2.
448. *See* Frakes & Wasserman, *supra* note 337, at 6; *see also* Moss, *supra* note 386.
449. *See generally* Frakes & Wasserman, *supra* note 330.

will exacerbate the problem by increasing the amount of prior art to review. As scientists subspecialize to cope with the burden of knowledge,[450] so should patent examiners, as a better equipped examiner may be more efficient. I-MAK proposes assembling a panel of non-examiners to assist in patent review, which is an ideal but likely impractical solution.[451] It is unclear who would select and train the panel in the relevant patent law concepts. The academic and industry researchers who currently volunteer to train patent examiners in the arts would likely be involved, but the proposed panel would require much more than the few days currently volunteered to the USPTO.[452] It is unlikely that academic and industry researchers would have the capacity to take on such time-consuming secondary commitments, and, without the very individuals most knowledgeable of incremental research, the panel loses value. Improving the current training program may be more practical. Moreover, limitations on repeat applications would be an effective means of mitigating concerns until more financial resources are available to expand and continuously train expert personnel.[453]

USPTO reform could improve shareholder initiatives to hold corporate management accountable for anticompetitive practices. Several major pharmaceutical and biotechnology companies received shareholders' proposals to increase disclosure of patenting and pricing decisions.[454] For example, Johnson & Johnson received a proposal to "establish and report on a process by which the impact of extended patent exclusivities on product access would be considered in deciding whether to apply for secondary . . . patents."[455] If implemented, the company would disclose cost-benefit analyses of decisions to apply for patents that cover, for example, new formulations and methods of use, considering the toll of high monopoly prices on public access to healthcare.[456] The board of directors opposed the proposal, noting that it already publishes a transparency report regarding pricing, but the report does not assess patents.[457] The USPTO can facilitate shareholders' goals by improving their searchable database, which is not

450. *See supra* Part II.B.2.

451. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 19, at 8.

452. *Patent Examiner Technical Training Program*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/patents/initiatives/patent-examiner-technical-training-program#step1 [https://perma.cc/7SJN-22CH] (last visited Feb. 9, 2024).

453. *See* Frakes & Wasserman, *supra* note 337, at 10.

454. Craig Wanda, *2024 Shareholder Proposals at Pharma Companies Cite Strategies to Keep Drug Prices High as Potential Human Rights Risks*, INTERFAITH CTR. CORP. RESP. (Dec. 14, 2023), https://www.iccr.org/2024-shareholder-proposals-at-pharma-companies-cite-strategies-to-keep-drug-prices-high-as-potential-human-rights-risks/ [https://perma.cc/B6XZ-RV7K].

455. JOHNSON & JOHNSON, 2023 PROXY STATEMENT AND ADDITIONAL DEFINITIVE PROXY SOLICITATION MATERIALS 136 (2023), https://www.investor.jnj.com/files/doc_financials/2022/ar/2023-proxy-statement.pdf [https://perma.cc/B4YE-8J5P].

456. *Id.*

457. *See id.* at 137. *See generally* JOHNSON & JOHNSON, THE 2022 JANSSEN U.S. PRICING TRANSPARENCY BRIEF (2023), https://transparencyreport.janssen.com/_document/2022-janssen-transparency-report-pdf?id=00000188-267e-d95e-abca-7e7e58750000.

easily analyzed by the general public.[458] A more user-friendly and comprehensive database, as proposed by I-MAK, would provide more data to monitor anticompetitive corporate practices.[459] Transparency can increase public scrutiny of corporate behavior and make it easier for consumers, competitors, and agencies to criticize exploitative conduct.

More transparency in the patent process can also improve regulation of antitrust violations. Corporate patent policies that have anticompetitive effects may be subject to antitrust limitations,[460] but these effects are often speculative and difficult for plaintiffs to show.[461] Moreover, companies can argue that procompetitive benefits outweighed the costs,[462] essentially completing the analyses requested in shareholder proposals.[463] User-friendly data sharing can support consumers by characterizing the relevant circumstances, such as impending patent cliffs, and potential legitimate business reasons. Improved USPTO monitoring and reporting of patent thickets can make antitrust law more responsive to patent misuse. Although patent law reforms risk broadly disincentivizing incremental R&D, antitrust law can target anticompetitive uses of incremental R&D with better precision and less risk to scientific progress.

CONCLUSION

Incremental innovation is too important to be deprived of robust patent protection. Although legal and regulatory reforms are necessary to limit manipulative practices, higher patentability standards pose an outsized threat to scientific progress. Instead, the best way for the USPTO to ensure the integrity of patent rights is to provide guidelines that reinforce well-established principles of scientific research, namely that minor improvements have value. There is insufficient consensus on when an improved drug, biologic, or medical use is obvious to try. Routine optimization generally precludes patent eligibility, but the standard misrepresents experimentation in the unpredictable arts. Clear and consistent patentability standards will facilitate other areas of reform and allow new governmental initiatives to endure the test of time.

458. *Patent Assignment Search FAQ*, U.S. PAT. & TRADEMARK OFF., https://assignment.uspto.gov/patent/index.html#/faq [https://perma.cc/S7UF-BPCM] (last visited Feb. 9, 2024).

459. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 19, at 3.

460. Fed. Trade Comm'n v. Actavis, Inc., 570 U.S. 136, 148 (2013) (holding that "patent and antitrust policies are both relevant in determining the 'scope of the patent monopoly'—and consequently antitrust law immunity").

461. *See supra* Part II.B.3.

462. *See* Mylan Pharms., Inc. v. Warner Chilcott Pub. Co., No. CV-12-3824, 2015 WL 1736957, at *5 (E.D. Pa. Apr. 16, 2015), *aff'd*, 838 F.3d 421 (3d Cir. 2016).

463. *See* JOHNSON & JOHNSON, *supra* note 455, at 136.