Unpatenting Product Hops

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On July 9, 2021, President Joseph R. Biden signed Executive Order 14036 ("Promoting Competition in the American Economy"), which directed the U.S. Food and Drug Administration (FDA) and the U.S. Patent and Trademark Office (USPTO) to collaborate on new approaches to increasing competition and lowering prices in the pharmaceutical marketplace. In response, the USPTO outlined several new initiatives, among them an intent to improve the robustness and reliability of issued patents.

A major impetus for the Executive Order was the pervasive nature of pharmaceutical product hopping, which occurs when manufacturers introduce new follow-on versions of lucrative pharmaceutical products to the market, versions of low added commercial value like extended-release forms of drugs, or modifications to device components of combination therapeutics. Product hops are usually intended to mitigate lost market share due to generic competition or thwart generic competition entirely. Yet the small benefits of these new products are usually far outweighed by excess costs to payers and patients alike. Product hops remain an essential part of product lifecycle management strategies due to patents, many of which are obtained after the flagship product is on the market and which offer market exclusivity for these incrementally better products. These patents also discourage manufacturers from entering lucrative markets, encourage settlement and delayed generic entry, and result in the prescribing of marginally better product hops at brand-name prices. In doing so, they undermine the fundamental constitutional intent of the patent system—a time-limited exclusive right.

Elevating patentability standards at the USPTO could mitigate product hopping through the rejection of weaker patents, which should eventually curtail patent applications from manufacturers that attempt to create "new," yet arguably uninventive, products intended primarily to capture market share from would-be competitors. This article evaluates the core elements of patentability and relevant case law, highlighting opportunities for the USPTO to strengthen its review of pharmaceutical patents. When coupled with regulatory reforms that

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further mitigate the impact of product hops, pharmaceutical research and development may pivot away from product life cycle management strategies that focus on extending the profitability of older drugs facing the prospect of generic competition and toward transformative innovation that accelerates the development of the next generation of therapeutics and cures.

INTRODUCTION

When a lucrative pharmaceutical product nears the end of its market exclusivity period, brand name manufacturers often pursue strategies aimed at mitigating losses incurred by generic entry. One such effort comes in the form of follow-on products, for which manufacturers obtain FDA approval and promote heavily, to drive prescribing away from generic products. This process is colloquially known as "product hopping" and has become a hallmark of the

incremental innovation that occurs when market exclusivity periods near their end.[1] Importantly, product hopping may be more cost-effective to brand manufacturers than the riskier biomedical innovation associated with the development of novel therapeutics.[2] For this reason, many companies devote substantial resources to "product lifecycle management" divisions responsible for extending market monopolies in both time-tested and creative ways.[3]

The anticompetitive nature of these practices has raised suspicion among both the Federal Trade Commission (FTC) and courts over the years.[4] The FTC has intervened to halt the abrupt market removal of lucrative brand name products prior to generic entry.[5] Abbott Laboratories' cholesterol medication TriCor, Warner-Chilcott's antimicrobial drug Doryx, and Forest Laboratories' dementia treatment Namenda are examples of this "hard switch" maneuver.[6]

To be fair, product hops can potentially serve some overarching public health benefit, such that additional revenues accruing to the brand name manufacturer could be justified given the net public health gains.[7] The most

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1. *See* Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167, 168 (2016) (explaining that a brand manufacturer engages in a "product hop" by combining two actions: (1) reformulating the product in a way that makes a generic version of the original product not substitutable, and (2) encouraging doctors to write prescriptions for the reformulated rather than the original product); *see also* Bret Dickey, Kun Huang & Daniel L. Rubinfeld, *Pharmaceutical Product Hopping: Is There A Role For Antitrust Scrutiny?*, 82 ANTITRUST L.J. 679, 680 (2019) ("Product hopping is broadly characterized as a branded manufacturer introducing a minor change to an existing prescription drug product and substantially shifting sales to the reformulated product, with the effect of inhibiting emerging competition from a generic version of the original branded product.").

2. Joshua Krieger, Danielle Li & Dimitris Papanikolaou, *Missing Novelty in Drug Development*, 35 REV. FIN. STUD. 636, 638 (2022) ("[N]ovel candidates are riskier investments: relative to other drug candidates developed in the same quarter for the same disease indication, 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."); *see also* Jose-Maria Fernandez, Roger M. Stein & Andrew W. Lo, *Commercializing Biomedical Research Through Securitization Techniques*, 30 NATURE BIOTECHNOLOGY 964, 964 (2012) ("[T]he lengthy process of biomedical innovation is becoming increasingly complex, expensive, uncertain and fraught with conflicting profit-driven and nonpecuniary motivations and public-policy implications.").

3. See Vandana Prajapati & Harish Dureja, *Product Lifecycle Management in Pharmaceuticals*, 12 J. MED. MKTG. 150, 151 (2012) ("Pharmaceutical companies are now determined to extend the life of their drug beyond patent expiration, devising strategies to manage the lifecycle of their most important medicines that begin in the clinical phases. [Product lifecycle management] has become a necessity to the continued success of pharmaceutical companies.").

4. *See* Dickey, et al., *supra* note 1, at 681 ("The Federal Trade Commission has expressed the view that 'minor, non-therapeutic changes to a branded pharmaceutical product that harm generic competition can constitute exclusionary conduct that violates U.S. antitrust laws.'").

5. So-called "hard switches" usually represent an attempt by the manufacturer to thwart market entry of generics by pushing its brand-name consumers over to a new, reformulated version of the product before generics are allowed to compete. By virtue of being non-interchangeable, those new products cannot be substituted for generics at a pharmacy level.

6. *See* Carrier & Shadowen, *supra* note 1, at 192–200. In contrast to a "hard switch," a "soft switch" occurs when a product hop is introduced but generics are not impeded from entering the market. *Id.* at 167. Carrier & Shadowen make the case for treating hard and soft switches similarly under antitrust. *Id.* at 211 ("[T]he no-economic-sense test . . . keeps the antitrust analysis focused on economic realities rather than any artificial distinctions between 'hard' and 'soft' switches.").

7. Michael S. Sinha, *Public Health Product Hops*, 73 AM. U. L. REV. 395 (2023) (exploring whether anticompetitive product hops could be justifiable because they advance public health objectives).

persuasive example of such a product manifested in the recent over-the-counter (OTC) switch of intranasal naloxone, the drug that can reverse respiratory suppression induced by opioid overdose.[8] Though prescription-to-OTC switches do not usually register as classic "product hops," they can often share features, including mitigation of generic competition and promotion premised on consumer preference for brand-name products. Other scholars have recently advocated for prescription-to-OTC switches of other medications for the benefit of public health, like the abortifacient mifepristone[9] and pre-exposure prophylaxis (PrEP) for the prevention of HIV.[10]

Yet such product hops that generate public health benefits sufficient to justify extended market monopolies and higher prices are the rare exceptions. In most cases, product hops offer small yet tangible benefits, the value of which is often difficult to quantify yet come with high price tags for both payers and patients. Moreover, they are implemented outside what Carrier and Shadowen call the "generic window," the period where generic entry is expected.[11] For good reason, product hops have received increased scrutiny from the FTC, and more recently, from Congress.[12] One of the driving forces behind the extension of market exclusivity for certain products is the curation of extensive patent portfolios, aimed at thwarting generic competition while fostering patent settlements in exchange for delayed generic or biosimilar product launches.

Many of these patents consist of what scholars would describe as secondary or tertiary patents. While the primary patent covers the chemical structure of the molecule itself, secondary patents cover aspects of a molecule, including stable salt formations, enantiomers, methods of use, and different methods of manufacture for a given compound, irrespective of whether those patents are used or applied to manufacture the marketed product.[13] For drug-device combinations, manufacturers have benefited from their pursuit of so-called tertiary patents, which have been described as patents covering the device component of the product, such as the delivery system.[14]

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8. *Id.* at 426.

9. Lewis A. Grossman, *Freedom Not to See a Doctor: The Path Toward Over-the-Counter Abortion Pills*, 2023 WISC. L. REV. 1041, 1049 (2023).

10. Douglas Krakower & Julia L. Marcus, *Free the PrEP—Over-the-Counter Access to HIV Preexposure Prophylaxis*, 389 NEW ENG. J. MED. 481, 482 (2023).

11. Carrier & Shadowen, *supra* note 1, at 207; *see also* Steve D. Shadowen, Keith B. Leffler & Joseph T. Lukens, *Anticompetitive Product Changes in the Pharmaceutical Industry*, 41 RUTGERS L.J. 1, 7 (2009) (Table 1 notes that ~80% (344/425) of product changes in the study occurred outside the "generic window.").

12. *See* S. 150, Affordable Prescriptions for Patients Act, 118th Cong. (2023) (seeking to prohibit product hopping by drug manufacturers).

13. See Amy Kapczynski, Chan Park & Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PLOS ONE, Dec. 2012, at 1; *see also* Cynthia M. Ho, *Should All Drugs Be Patentable?: A Comparative Perspective*, 17 VAND. J. ENT. & TECH. L. 295, 313 (2015) ("Secondary patents may cover peripheral features such as a tablet coating, an intermediate product that naturally results after ingesting the drug, or methods of use; it could also include a different dosage or delivery route.").

14. Michael S. Sinha, *Costly Gadgets: Barriers to Market Entry and Price Competition for Generic Drug-Device Combinations in the United States*, 23 MINN. J. L. SCI. & TECH. 293, 311 (2022); *see also* Reed F. Beall & Aaron S. Kesselheim, *Tertiary Patenting on Drug-Device Combination Products in the United States*, 36 NATURE BIOTECHNOLOGY 142, 142 (2018); Reed F. Beall, Jason W. Nickerson,

In recent years, the number of patents that accrue to a lucrative brand-name drug, including follow-on products that the manufacturer seeks to market, has been astonishingly high.[15] Incremental innovation, followed by patenting of those innovations, has been a primary driver of not only product hops, but also the high prices associated with non-novel, obvious, or only modestly useful product innovations.

I. ADDRESSING PRODUCT HOPPING THROUGH THE PATENT SYSTEM

A primary driver of product hopping is the pursuit of patent protection for follow-on products. With that additional protection in hand, manufacturers will obtain FDA approval for incrementally innovative products, like extended-release formulations of drugs, that either limit market entry of competitors or compete for market share with generic entrants. Many of the patents covering these products are weaker than patents on base compounds, in that they are more likely to be invalidated in patent infringement litigation.[16] But since invalidation implies that the patents were inappropriately issued by the USPTO, a better avenue for reform may be to strengthen standards at the Patent Office to limit the number of these patents that are issued.[17] This way, manufacturers will have less incentive to pursue product hops since their follow-on products will lack the benefit of patent protection.

In response to the ongoing challenges associated with high drug pricing, on July 9, 2021, President Joseph R. Biden signed an Executive Order 14036 ("Promoting Competition in the American Economy"), stating that "too often, patent and other laws have been misused to inhibit or delay—for years and even decades—competition from generic drugs and biosimilars, denying Americans access to lower-cost drugs."[18] In the Executive Order, the Biden Administration asked the FDA and the USPTO to work together on solutions to increase competition in the pharmaceutical marketplace and lower the price of prescription drugs.[19] In response, the USPTO outlined several new initiatives, among them one

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Warren A. Kaplan & Amir Attaran, *Is Patent "Evergreening" Restricting Access to Medicine/Device Combination Products?*, 11 PLOS ONE 1 (2016).

15. *The Truth About America's Top Selling Drugs in 2021*, I-MAK, https://www.i-mak.org/2021-top-selling [perma.cc/J8XW-MXEP] (last visited Feb. 1, 2025).

16. S. Sean Tu & Mark A. Lemley, *What Litigators Can Teach the Patent Office About Pharmaceutical Patents*, 99 WASH. U. L. REV. 1673, 1673 (2022).

17. Victor L. Van de Wiele, Aaron S. Kesselheim & S. Sean Tu, *Biologic Patent Challenges Under the America Invents Act*, 42 NATURE BIOTECHNOLOGY 374, 374 (2024); *see also* Jorge L. Contreras & Arti K. Rai, *Orange Book Over-Declaration of Pharmaceutical Patents: The Advantages of Ex Ante Over Ex Post Review*, HEALTH AFFS. FOREFRONT (Dec. 13, 2023), https://www.healthaffairs.org/content/forefront/orange-book-over-declaration-pharmaceutical-patents-advantages-ex-ante-over-ex-post [perma.cc/X648-YYDF].

18. Exec. Order No. 14,036, 86 Fed. Reg. 36987, 36988 (July 9, 2021) ("[T]o help ensure that the patent system, while incentivizing innovation, does not also unjustifiably delay generic drug and biosimilar competition beyond that reasonably contemplated by applicable law, not later than 45 days after the date of this order, through the Commissioner of Food and Drugs, write a letter to the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office enumerating and describing any relevant concerns of the FDA." *Id.* at 36997).

19. *Id.*

that aims to "improv[e] procedures for obtaining a patent to ensure that the USPTO issues robust and reliable patents."[20]

How should the USPTO go about addressing this problem? This piece explores approaches to disincentivizing the pursuit of product hops through more stringent review of patentability standards at the Patent Office. Though the USPTO's rulemaking authority is procedural and not substantive,[21] John M. Golden notes that "the USPTO can accomplish much to improve the workings of patent law by using its existing fact-finding and non-binding rulemaking powers."[22] Even if agency actions can be challenged in court, "USPTO interpretations of substantive patent law can stand for years without facing serious challenge."[23] That said, the recommendations offered here should be interpreted in a manner consistent with these limits on USPTO regulatory authority.

II. PATENTABLE SUBJECT MATTER

Under 35 U.S.C. § 101, "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" is patentable.[24] At first glance, patents covering product hops seem likely to meet standards for subject matter eligibility. Just like the primary patent covering the active component of the pharmaceutical, secondary patents covering salts or enantiomers would clearly be subject matter eligible as compositions of matter.

Yet the Supreme Court decided a quartet of cases in the early 2010s that complicated the state of subject matter eligibility.[25] The resulting test that emerged from those decisions, the *Mayo/Alice* two-step, created confusion among many as to whether certain types of inventions would still be patentable even if they did not fit into statutorily defined categories.[26] The two-step test requires asking (1) whether the claims are "directed to" unpatentable subject matter; and (2) whether an "inventive concept" elevates the subject matter through the creation of new and useful applications of natural phenomena.[27]

A. Mayo *and Method of Treatment Patents*

The *Mayo v. Prometheus* decision is particularly relevant to secondary pharmaceutical patents that describe a method of use. The Court invalidated a method-of-use patent that described how a physician should interpret a laboratory

20. *What Are USPTO-FDA Collaboration Initiatives?*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/initiatives/fda-collaboration/what-are-uspto-fda-collaboration-initiatives [perma.cc/QEX4-HBN4] (last visited Feb. 1, 2025).

21. *See* 35 U.S.C. § 2(b)(2); *see also* Cooper Techs. Co. v. Dudas, 536 F.3d 1330, 1335 (Fed. Cir. 2008) ("To comply with section 2(b)(2)(A), a Patent Office rule must be 'procedural'-i.e., it must 'govern the conduct of proceedings in the Office.'").

22. John M. Golden, *The USPTO's Soft Power: Who Needs Chevron Deference*, 66 SMU L. REV. 541, 543 (2013).

23. *Id.* at 557.

24. 35 U.S.C. § 101.

25. Bilski v. Kappos, 561 U.S. 593 (2010); Mayo Collaborative Services v. Prometheus Labs, 566 U.S. 66 (2012); Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013); Alice Corp. v. CLS Bank Int'l, 573 U.S. 208 (2014).

26. EMILY G. BLEVINS & KEVIN J. HICKEY, CONG. RSCH. SERV., IF12563, PATENT-ELIGIBLE SUBJECT MATTER REFORM: AN OVERVIEW (2024).

27. *Id.*

result and adjust a patient's medication dose (up or down) accordingly to achieve a desired therapeutic range.[28] The Court found the patent to cover an abstract idea but held that "the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' or adding 'insignificant postsolution activity.'"[29]

Since the *Mayo* decision, the Federal Circuit has encountered several cases pertaining to method of treatment patents, with mixed results as to patent eligibility.[30] In the 2017 case *Cleveland Clinic Found. v. True Health Diagnostics LLC*, the Federal Circuit invalidated a patent claiming methods for detecting the blood level of an enzyme known to be an early indicator of cardiovascular disease and correlating that lab result with risk of cardiovascular disease.[31] The court found that the patents were directed to laws of nature but did not find an inventive concept.[32]

Then in the 2018 decision *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International, Ltd.*, the Federal Circuit applied the *Mayo/Alice* two-step to a patent covering a method of treating schizophrenia.[33] Despite similarities to *Mayo*, the Federal Circuit determined that the claims at issue were not directed to ineligible subject matter, and therefore, *Mayo/Alice* did not apply.[34] In 2019, the Federal Circuit in *Athena Diagnostics, Inc. v. Mayo Collaborative Services* determined that a method of diagnosing a disease by identifying the presence of a certain antibody was not patent eligible.[35] The court distinguished its 2018 holding in *Vanda*: "[N]ote the difference between the claims before us here, which recite a natural law and conventional means for detecting it, and applications of natural laws, which are patent-eligible."[36] In a second Federal Circuit decision in 2019, *Natural Alternatives International v. Creative Compounds, LLC*, the court noted more definitively, "[t]hese are treatment claims and as such they are patent eligible."[37] Consistent with post-*Mayo* Federal Circuit case law,[38] the USPTO should reject patent claims that merely direct a physician to apply routine principles of clinical

28. *Mayo*, 566 U.S. at 74–75.

29. *Id.* at 73 (quoting Diamond v. Diehr, 450 U.S. 175, 191–92 (1981)).

30. Timothy P. McAnulty & Emily R. Gabranski, *Excluded Subject-Matter the U.S. Way*, 48 CIPA J. 29 (2019).

31. Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352, 1355 (Fed. Cir. 2017).

32. *Id.* at 1362 ("In *Ariosa*, the challenged claims involved a method that was a general instruction to doctors to apply routine, conventional techniques when seeking to detect paternally inherited cell-free fetal DNA in the blood serum of a pregnant woman. *Ariosa*, 788 F.3d at 1377. The same is true here.").

33. Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd., 887 F.3d 1117, 1117 (Fed. Cir. 2018).

34. *Id.* at 1133–34.

35. Athena Diagnostics, Inc. v. Mayo Collaborative Servs., 915 F.3d 743 (Fed. Cir. 2019).

36. *Id.* at 752.

37. Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC, 918 F.3d 1338, 1344 (Fed. Cir. 2019) (This was distinguished by a very recent Federal Circuit case in 2024, which held that a method of manufacture claim was patent ineligible as a natural phenomenon or abstract idea. PureCircle USA Inc. v. SweeGen, Inc., No. 2022-1946, 2024 WL 20567 (Fed. Cir. Jan. 2, 2024)).

38. The Supreme Court denied certiorari in three of the four cases, allowing the decisions to stand—the exception is *Natural Alternatives International*, which has not been appealed to date. Cleveland Clinic Found. v. True Health Diagnostics LLC, 584 U.S. 1032 (2018); Hikma Pharms. USA Inc. v. Vanda Pharms. Inc., 140 S. Ct. 911 (2020); Athena Diagnostics, Inc. v Mayo Collaborative Servs., 140 S. Ct. 855 (2020).

medicine as laws of nature.[39]As the Court in *Mayo* aptly noted, "[t]o transform an unpatentable law of nature into a patent-eligible application of such law, one must do more than simply state the law of nature while adding the words 'apply it.'"[40]

By more closely scrutinizing such patents, the USPTO can reject weak method of treatment patents, which may have the effect of thinning patent portfolios while discouraging future patent applications claiming such methods.[41] The FDA can aid USPTO in determining the impact of such patents on market exclusivity extensions or product hops in the pipeline. Perhaps this could discourage valuable incremental innovation via "indication-mining" for supplemental uses, which may limit the extent to which manufacturers study and identify secondary uses for approved drugs.[42] Yet it would also decrease the sometimes-substantial costs of follow-on studies—in some notable instances, the costs of indication-mining studies are exorbitant and difficult to justify.[43]

B. Myriad Genetics *and the Downstream Effects of* Myriad

Another major Supreme Court case on subject matter eligibility, *Association for Molecular Pathology v. Myriad Genetics, Inc.*, was decided in 2013.[44] The Court held that isolated human genes and DNA sequences could not be patented because they were naturally occurring. Several bills have been proposed in Congress to overturn the holding in this case, including the Patent Eligibility Restoration Act of 2023.[45] As a senior staff attorney at the American Civil Liberties Union notes of the proposed bill, "[t]his legislation is a gift to patent lawyers and predatory companies while risking the creation of a disturbing market for exclusive rights over material found in nature and abstract ideas."[46] FDA and USPTO officials should consider articulating their opposition to this bill, as it conflicts with the objectives set forth in President Biden's Executive Order.

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39. *See* Cleveland Clinic Found. v. True Health Diagnostics, Inc., 859 F.3d 1352, 1362 (Fed. Cir. 2019) (explaining that "a general instruction to doctors to apply routine, conventional techniques" is not patent eligible).

40. Mayo Collaborative Servs. v. Prometheus Labs, 566 U.S. 66, 66 (2012).

41. *See* S. Sean Tu & Ameet Sarpatwari, *A "Method of Use" to Prevent Generic and Biosimilar Market Entry*, 388 NEW ENG. J. MED. 483, 483 (2023). (Notably, Tu and Sarpatwari call for action by the Supreme Court and Congress to address the issue in the context of "skinny labeling." *Id.* at 485.).

42. As part of product lifecycle management strategies, "indication-mining" refers to the practice of identifying and studying new uses that can extend market exclusivity and can be extremely promising, especially if they are "orphan indications." *See* Michael S. Sinha, Ariel D. Stern & Arti K. Rai, *Four Decades of Orphan Drugs and Priorities for the Future*, 391 NEW ENG. J. MED. 100, 100 (2024) ("Bevacizumab (Avastin) was first approved for a nonorphan indication and subsequently approved for 11 orphan indications.").

43. *See* Carole A. Federico, Taiji Wang, Adélaïde Doussau, Jeffrey S. Mogil, Dean Fergusson & Jonathan Kimmelman, *Assessment of Pregabalin Postapproval Trials and the Suggestion of Efficacy for New Indications: A Systematic Review*, 179 JAMA INTERNAL MED. 90, 95 (2019) ("Our analysis demonstrates that the blockbuster status of pregabalin in practice was accompanied by a large volume of research aimed at applying pregabalin to at least 33 new indications. Whether measured in number of trials or indications, much of this activity appears aimed at exploring the efficacy of pregabalin rather than proving it.").

44. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 576 (2013).

45. S. 2140, 118th Cong. (2023).

46. Press Release, American Civil Liberties Union, ACLU Opposes Legislation to Enable Patents on Human Genes (Aug. 3, 2022), https://www.aclu.org/press-releases/aclu-opposes-legislation-enable-patents-human-genes [perma.cc/6AAB-VXYJ].

While determining isolated sequences of DNA to be unpatentable, the *Myriad* decision did permit cDNA to be patented. cDNA is transcribed from naturally occurring mRNA, meaning it contains coding sequences for proteins produced from certain genes. The novel mRNA vaccines for COVID-19, and the patents protecting that technology, raise questions as to whether synthetically created mRNA should be treated more like cDNA (patent eligible) or like DNA (patent ineligible.)[47]

Given the patent estates held by Moderna, Pfizer, and BioNTech and the potential implications for extending patent eligibility to specific sequences of mRNA coding for products found in nature (e.g., the mutated spike protein of the SARS-CoV-2 virus that causes COVID-19), the USPTO should read the holding in *Myriad* to mean that mRNA-directed claims are patent ineligible as products of nature because the mRNA sequences naturally occur when the SARS-CoV-2 virus replicates.[48]

III. NOVELTY

To be patentable, inventions must be novel.[49] This requires a showing that the invention has not been previously disclosed, in either a prior patent or other publicly accessible format. After passage of the America Invents Act of 2011, there was concern that given the reshuffling of categories in 35 U.S.C. § 102 that make up the prior art, precedent would not be applicable to novelty jurisprudence moving forward.[50] The 2019 Supreme Court decision in *Helsinn Healthcare S.A. v. Teva Pharmaceuticals USA, Inc.* clarified that despite these statutory language changes, judicial precedent for patent novelty remained good law.[51]

The novelty question, as it relates to product hopping, is whether prior art in earlier patents or products disclosed the secondary compound in question, thereby precluding the patentee from obtaining a patent on the compound later. The primary arbiter here is whether the structure was publicly disclosed, thereby triggering the one-year grace period. In the case of an earlier patent, the clock would only begin ticking after the patent was published (eighteen months after filing),

47. Aparajita Lath, *Is Messenger RNA Patent-Eligible?*, BILL OF HEALTH BLOG (July 6, 2023), https://blog.petrieflom.law.harvard.edu/2023/07/06/is-messenger-rna-patent-eligible/ [perma.cc/VG7R-ZL4W] ("Amid ongoing patent disputes over the mRNA platform, a significant scientific question remains unanswered: whether mRNA itself even is patent-eligible.").

48. *See* Jorge Contreras, *Another Legislative Attempt to Revive Gene Patenting*, BILL OF HEALTH BLOG (Aug. 4, 2022), https://blog.petrieflom.law.harvard.edu/2022/08/04/another-legislative-attempt-to-revive-gene-patenting/ [perma.cc/5KW4-KCG3] ("[T]he unavailability of patents on genomic sequences has enabled researchers around the world to study the SARS-CoV-2 viral genome without fear of patent infringement and without the need to negotiate complex patent licensing agreements and pay royalties to the first researchers to determine its sequence.").

49. 35 U.S.C. § 102. The terms "novelty" and "anticipation" are often used interchangeably.

50. The categories of prior art before the America Invents Act were modified to include a new catch-all phrase, "matter otherwise publicly available." In *Helsinn Healthcare*, the Supreme Court declined to ascribe new meaning to AIA revisions to § 102 that would overturn a "settled body of law." Helsinn Healthcare v. Teva Pharms., 586 U.S. 123, 131 (2019).

51. *Id.* at 633–34. ("In light of this settled pre-AIA precedent on the meaning of 'on sale,' we presume that when Congress reenacted the same language in the AIA, it adopted the earlier judicial construction of that phrase.").

unless that patent was based on an earlier public disclosure that also characterized the secondary compound.[52]

A. Novelty of Enantiomers

Many drugs on the market are chiral molecules, meaning that they naturally exist as racemic mixtures of two mirror-image forms called enantiomers.[53] Sometimes enantiomers exert different biological effects, meaning that "pharmaceutical companies may want to market a drug containing only the more active enantiomer, even if its mirror image has been disclosed or even previously patented."[54] In his 2007 article "The Patentability of Enantiomers," Jonathan J. Darrow highlights the extent to which manufacturers pivoted to developing enantiomers: "[A] survey of 1,200 drugs under development worldwide disclosed that 820 were chiral and, of those, 610 were being developed as single enantiomers."[55]

But should enantiomers be considered novel under 35 U.S.C. § 102 under the theory of inherent anticipation?[56] Consider the example of the racemic mixture omeprazole [Prilosec] and its enantiomer esomeprazole [Nexium]. AstraZeneca made a chiral switch product hop, transitioning patients from the "purple pill" (omeprazole) to "the new purple pill" (esomeprazole).[57]

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52. There are three potentially relevant dates here: (1) the filing date, (2) the publishing date (eighteen months after the filing date), and (3) the date of issuance. Though the AIA encourages early disclosures by the inventor, the published application may still represent the first public disclosure of the secondary chemical structure.

53. Enantiomers are compounds that are structurally identical, except that they have opposite three-dimensional shapes. Because of this, only one enantiomer may be biologically active in a given compound. Racemic mixtures are 50:50 mixtures of two enantiomers, often resulting from the nonspecific synthesis of a particular drug. Compounds that can exist as mirror images are often described as chiral. *See* Jonathan McConathy & Michael J. Owens, *Stereochemistry in Drug Action*, 5 PRIMARY CARE COMPANION J. CLINICAL PSYCHIATRY 70, 72 (2003) ("The 2 enantiomers of a chiral drug may differ significantly in their bioavailability, rate of metabolism, metabolites, excretion, potency and selectivity for receptors, transporters and/or enzymes, and toxicity.").

54. Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2, 3 (2007).

55. *Id.*; *see also* Aaron S. Long, Audrey D. Zhang, Caitlin E. Meyer, Alexander C. Egilman, Joseph S. Ross & Joshua D. Wallach, *Evaluation of Trials Comparing Single-Enantiomer Drugs to Their Racemic Precursors: A Systematic Review*, 4 JAMA NETWORK OPEN, May 2021, at 1, 11 (2021) ("[N]ewly marketed, FDA-approved single-enantiomer drugs are infrequently directly compared with racemic precursors, and when they are, they are uncommonly found to provide improved efficacy or safety. These findings raise concerns about the greater costs to the health care system incurred by chiral switching, without evidence to support benefit to patients.").

56. Dan L. Burk & Mark A. Lemley, *Inherency*, 47 WM. & MARY L. REV. 371, 372 (2005) ("[T]he inherency doctrine permits defendants to invalidate a patent by showing that even though the prior art did not expressly disclose what the patentee claims to have invented, all or part of the patentee's invention was inherent in a particular piece of prior art."); *see also* Schering Corp. v. Geneva Pharms., Inc., 275 F. Supp. 2d 534, 541 (D.N.J. 2002), *aff'd sub nom.*, Schering Corp. v. Geneva Pharms., 339 F.3d 1373 (Fed. Cir. 2003) ("[K]nowledge or appreciation of that which anticipates need not be contemporaneous with the application for or issuance of the patent under scrutiny . . . a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it.").

57. ALEX BRILL, THE COST OF BRAND DRUG PRODUCT HOPPING (2020), https://www.optum.com/content/dam/optum3/optum/en/resources/PDFs/3505955-thought-leadership-cost-of-product-hopping-sept2020.pdf [perma.cc/3WEG-HGC4]; *see also* Israel Agranat & Hili Marom, *In*

1. Esomeprazole: Disclosure in Prior Art Patent

Separate from the issue of nonobviousness (discussed *infra* Section V), the question I posit here is whether the enantiomer had been disclosed in the primary patent, which should foreclose its patentability at a later date.

The United States patent for omeprazole details the following molecular structure that reveals chirality.[58]

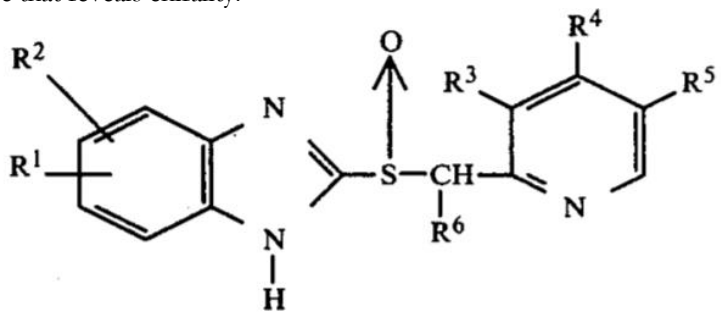

Figure 1

The arrow between the sulfur (S) and oxygen (O) moieties tells the "person having ordinary skill in the art" (PHOSITA) that omeprazole is a racemic mixture of two enantiomers. The Canadian patent for omeprazole is even clearer (Figure 2), explicitly detailing that there are two enantiomers.

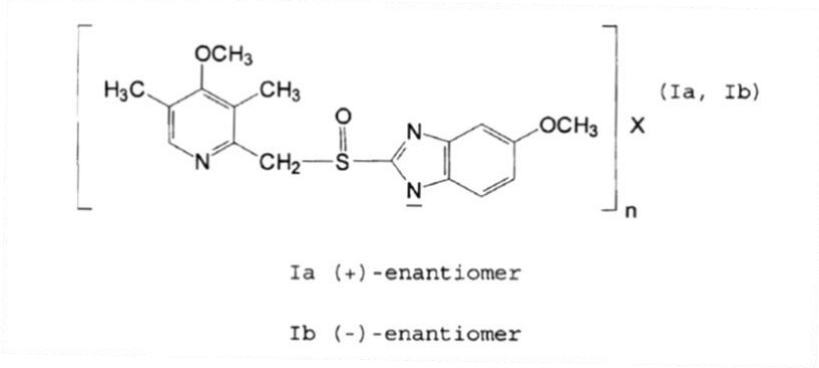

Figure 2[59]

In Canada, a court upheld AstraZeneca's patent covering esomeprazole as novel despite its structure having been clearly revealed in the earlier patent.[60]

Defense of Secondary Pharmaceutical Patents in Drug Discovery and Development, 11 ACS MED. CHEMISTRY LETTERS 91, 93–94 (2020).

58. U.S. Patent No. 4,255,431 (filed Apr. 5, 1979).

59. Canadian Patent No. 2,139,653 (filed May 27, 1994).

Interestingly, there are four structural variants of omeprazole, reflecting isomers and tautomers. See Agranat & Marom, *supra* note 57, at Figure 1.

60. AstraZeneca Canada Inc. v. Apotex Inc., [2017] 1 S.C.R. 943 (Can.). The esomeprazole patent was initially invalidated on utility grounds by the Federal Court, upheld by the Federal Court of Appeal, but overturned by the Supreme Court of Canada.

1. Esomeprazole: "On sale" Bar

Another potential bar to patentability for esomeprazole may be that the product was technically on sale (as part of omeprazole) since omeprazole's initial FDA approval in 1989.[61] In *Pfaff v. Wells Electronics*, the Supreme Court held that the on-sale bar had two requirements: (1) a "commercial offer for sale"; and (2) readiness for patenting, which could include reduction to practice or "drawings or other descriptions . . . sufficiently specific to enable a [PHOSITA] to practice the invention."[62]

Following this argument, esomeprazole was both for sale (as a component of omeprazole) and ready for patenting (since its structure had been revealed in the patent for omeprazole). Despite being cleverly marketed to patients as "the new purple pill," Nexium was not new at all, as most patients being switched to the drug had already been taking esomeprazole for years as part of Prilosec.[63] Even if a court held that the "on sale" bar did not apply on technical grounds, it would have to acknowledge that Nexium was "otherwise available to the public" as part of Prilosec under the inherency doctrine, even if the product label did not explicitly acknowledge its presence.[64]

B. Novelty of Prodrugs/Metabolites[65]

In another case involving the antihistamine loratadine [Claritin], the Federal Circuit in 2003 determined that the active form of the drug, descarboethoxyloratadine (DCL, or desloratadine), formed under normal conditions after the patient ingested the pill, resulting in inherent anticipation that precluded patenting of the compound.[66] That is, the company's patent for the metabolite was invalidated because DCL was necessarily disclosed by the original patent for loratadine: "DCL is not formed accidentally or under unusual conditions when loratadine is ingested. The record shows that DCL necessarily and inevitably

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61. Omeprazole [Prilosec] delayed release capsules were approved on September 14, 1989 (NDA 19-810). Of note, enantiomer patents often get around these technicalities by claiming a new composition with a certain purity of product (e.g., a 90% (+) form of the drug) as opposed to a racemic mixture with 50% (+) and 50% (-) forms. *See* John J. Cahill, Jr., *Patent Claim Construction of Enantiomers*, 15 TUL. J. TECH. & INTELL. PROP. 61, 67, 70 (2012) (noting that unequal mixtures confer unique physical properties such as optical activity to mixtures, and concluding that "for the purposes of novelty, a claim disclosing a composition that reflects the percentage of each enantiomer present in a nonequimolar mixture may be distinguished from its previously existing racemate.").

62. Pfaff v. Wells Electronics, Inc., 525 U.S. 55, 67-68 (1998).

63. See Michael A. Carrier, *A Simple Solution to the Problem of "Product Hopping*," HARV. HEALTH POL'Y REV., 2021, at 1 ("AstraZeneca 'launched a massive advertising and detailing campaign designed to persuade doctors and consumers that Nexium was a significant improvement over Prilosec.'") (quoting First Amended Complaint, Walgreen Co. v. AstraZeneca Pharms. LP, 534 F. Supp. 2d 146 (D.D.C. 2008)).

64. 35 USC § 102(a).

65. A prodrug is a chemical compound that does not have biological activity unless it is metabolically activated in the body, such as through exposure to the acidic environment of the stomach. *See* V. Stella, *Pro-Drugs: An Overview and Definition*, 14 ACS SYMP. SERIES 1, 1 (1975) (The term "describe[s] compounds which undergo biotransformation prior to exhibiting their pharmacological effects.").

66. Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373 (Fed. Cir. 2003).

forms from loratadine under normal conditions. DCL is a necessary consequence of administering loratadine to patients."[67]

At the time, studies pointed to the use of metabolites like DCL for patients who could not tolerate side effect profiles of earlier derivatives that were overly sedating.[68] DCL was approved in 2001 and sold under the brand name Clarinex.

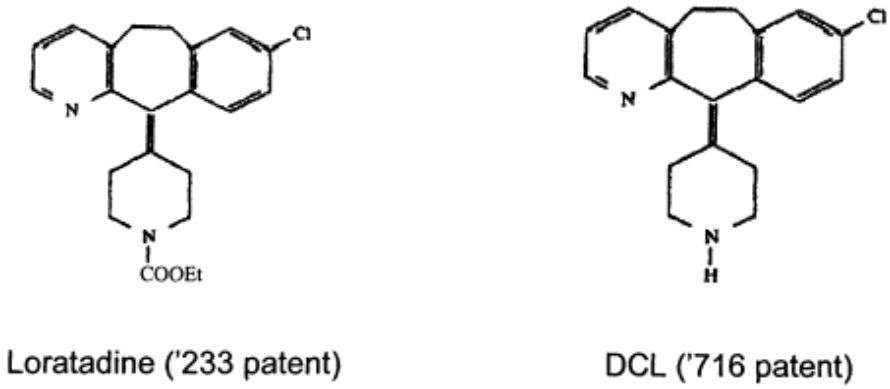

Figure 3: Chemical structures of loratadine and DCL

C. Novelty of Method of Manufacturing Patents

Secondary patents for lucrative brand-name drugs may also include methods of manufacturing the drug. Given their relative complexity, biologics are more likely to have such patents in their patent portfolios as compared to small molecule drugs. Yet biosimilar manufacturers often struggle to produce exact replicas of the originator biologic compound because producing a biologic often requires a full understanding of a plethora of patents and trade secrets.

W. Nicholson Price and Arti K. Rai make the case for invalidating such patents under the principle established by Judge Learned Hand in his famous 1946 decision *Metallizing Engineering Co. v. Kenyon Bearing & Auto Parts Co*.: "[C]ommercial use of a manufacturing process counts as a patent-defeating 'public use' even if the process is kept secret."[69] Price and Rai divide method-of-manufacture patents into ones obtained pre-launch and post-launch, asserting that biologic manufacturers must have used pre-launch methods of manufacture at least one year prior to approval, which would render the method unpatentable as a secret public use.[70] Post-launch methods, because they were not used to make the biologic at its launch,

67. *Id.* at 1378.

68. David Murdoch, Karen L. Goa & Susan J. Keam, *Desloratadine: An Update of its Efficacy in the Management of Allergic Disorders*, 63 DRUGS 2051, 2051 (2003). Clarinex was approved by the FDA on December 21, 2001. CTR. FOR DRUG EVALUATION AND RSCH., APPROVAL PACKAGE FOR: APPLICATION NUMBER 21-165 (2001), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-165_Clarinex_Approv.pdf [perma.cc/2FV7-2CAD].

69. W. Nicholson Price & Arti K. Rai, *How Logically Impossible Patents Block Biosimilars*, 37 NATURE BIOTECHNOLOGY 862 (2019) (citing Metallizing Engineering Co. v. Kenyon Bearing & Auto Parts Co., 153 F.2d 516 (2d Cir. 1946)).

70. *Id.*

should not be used to block biosimilar versions.[71] As such, they describe such patents as "logically impossible," calling for their invalidation.[72]

That said, shifting to newer, cutting-edge methods of manufacture post-launch may seem appealing or even desirable. Companies may conduct bridging studies to validate a more efficient method of manufacture during the market exclusivity period as part of routine follow-on research and development. But Robin Feldman, pointing to the century-long market dynamics of insulin products, highlights that incremental improvements in insulin analogues or devices, followed by discontinuation of older products, generate new periods of market exclusivity and profitability while blocking a "trailing edge" of older, more affordable versions that could bring down costs.[73]

Perhaps the most important consequence of curtailing the patentability of post-launch methods might be the move to trade secrecy. Feldman notes in earlier work that for biologics, patents may clash with trade secrets, producing an information vacuum for follow-on manufacturers via the exclusion of essential information for manufacturing a drug or biologic.[74] This became a particularly contentious issue during COVID-19, where many argued that even open licensing or placement of patents for mRNA vaccines in patent pools would not be sufficient to allow others to manufacture vaccines elsewhere given the existence of "company know-how" via trade secrets.[75]

IV. NONOBVIOUSNESS

Obviousness is perhaps the clearest point in patentability where secondary patent applications could be more closely scrutinized by the USPTO. Section 103 of the Patent Act reads in relevant part:

> A patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been

71. *Id.*

72. *Id.* at 863 ("[A]lthough these logically impossible patents are likely to represent a substantial fraction of patent thickets, the thickets overall are quite formidable, and potential competitors must cut through the entire thicket to win market entry.").

73. Robin Feldman, *Cutting-Edge Insulin is Good. But it's the 'Trailing Edge' of Older Versions That Can Keep It Affordable*, STAT NEWS (May 15, 2024), https://www.statnews.com/2024/05/15/discontinuing-insulin-problematic-trailing-edge-older-versions-keep-it-affordable [perma.cc/N7R9-598V].

74. Robin Feldman, *Trade Secrets in Biologic Medicine: The Boundary with Patents*, 24 COLUM. SCI. & TECH. L. REV. 1, 27 (2022) ("[C]ompanies might submit claims on manufacturing processes that contain a range of values for such critical facets of drug batch manufacture as temperature and concentration. Alternatively, a company might submit claims that include an extremely wide variety of possible means of manufacture, even the type of host cell . . . in which a drug might be produced.").

75. *See* Siva Thambisetty, Aisling McMahon, Luke McDonagh, Hyo Yoon Kang & Graham Dutfield, *Addressing Vaccinee Inequity During the COVID-19 Pandemic: The TRIPS Intellectual Property Waiver Proposal and Beyond*, 81 CAMBRIDGE L.J. 384, 396 (2022) ("[I]nadequate patent disclosures, combined with trade secrets and tacit know-how, can obscure the theoretically assumed balance between IP restrictions and the public interest."); *see also* Michael S. Sinha, Sven J.R. Bostyn & Timo Minssen, *Addressing Regulatory Exclusivity Issues During the COVID-19 Pandemic*, *in* COVID-19 AND THE LAW: DISRUPTION, IMPACT, AND LEGACY 249 (I. Glenn Cohen, Abbe D. Gluck, Katherine Kraschel & Carmel Shachar eds., 2023).

> obvious . . . to a person having ordinary skill in the art to which the claimed invention pertains.[76]

Under the nonobviousness doctrine, even if the molecule itself was not disclosed in the prior art, a PHOSITA would recognize the invention of the secondary compound as obvious based on the prior art.

A. Pre-KSR

Prior to the 1952 Patent Act, a patentable invention required "more ingenuity and skill . . . than that possessed by an ordinary mechanic acquainted with the business."[77] Unlike anticipation, where every aspect of an invention must exist in a single prior art reference, nonobviousness permits the PHOSITA to use multiple references to get to the claimed invention. As Judge Giles Rich noted in 1966, "We think the proper way to apply the [§] 103 obviousness test to a case like this is to first picture the inventor as working in his shop with the prior art references—which he is presumed to know—hanging on the walls around him."[78]

In *Cuno Engineering*, that standard was elevated to require a "flash of creative genius, not merely the skill of the calling."[79] The *Graham v. John Deere* case altered the nonobviousness doctrine considerably, articulating a series of secondary considerations that continue to be relevant post-*KSR*.[80] These secondary considerations include commercial success, long felt but unsolved need, failure of others, licensing, copying, acclaim, teaching away, and unexpected results.[81]

After *Graham*, the Federal Circuit shifted toward a test that required "a suggestion, teaching, or motivation to combine the prior art references" coupled with "a reasonable expectation of success."[82] Objective evidence, such as those in the *Graham* secondary considerations, remained a critical element of the nonobviousness determination.[83]

B. KSR v. Teleflex

In the landmark 2007 Supreme Court decision *KSR International Co. v. Teleflex Inc.*, the Court rejected the "rigid approach" of the Federal Circuit, instead articulating what it considered to be a more flexible "reason to combine" standard.[84] The "reason to combine" analysis should be made explicit, although any objective reason can suffice.[85] The Court also noted that predictable combinations were suspect: "[T]he combination of familiar elements according to known methods is

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76. 35 U.S.C. § 103.

77. Hotchkiss v. Greenwood, 52 U.S. 248, 265 (1851).

78. *In re* Winslow, 365 F.2d 1017, 1020 (C.C.P.A. 1966).

79. Cuno Eng'g Corp. v. Automatic Devices Corp., 314 U.S. 84, 91 (1941).

80. Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 1 (1966).

81. *Id.* at 17; *see also* United States v. Adams, 383 U.S. 39, 51–52 (1966).

82. Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124–25 (Fed. Cir. 2000).

83. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986) ("Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached and is not merely 'icing on the cake,' as the district court stated at trial.").

84. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007).

85. *Id.*

likely to be obvious when it does no more than yield predictable results."[86] In addition, upgrades are often obvious: "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."[87]

Though the *KSR* case focused on brake pedals, the outcome generated concern among some in the pharmaceutical industry.[88] As norms for pharmaceutical development emerged across the industry, the concern became "obvious to who?" The following are clinical examples that could be seen as obvious depending on who is tasked with making that determination (i.e., the PHOSITA).

1. Combination Medications: HAART

Highly active antiretroviral therapy (HAART) for HIV was a crucial development in treating the condition. Yet nonadherence could also lead to drug resistance, so it was paramount that patients took their medications regularly. In an effort spearheaded by businessman and long-time CEO of Gilead Sciences, John C. Martin, the once-daily pill for HIV therapy emerged as an effort to increase compliance and decrease drug resistance.[89] By portraying HIV and AIDS patients as less responsible, pharmaceutical manufacturers, policymakers, and even the National Institute of Allergy and Infectious Diseases (NIAID) (see Figure 4), persuaded physicians that adherence would increase with combination pills by reducing pill burden for HIV patients. However, this also allowed for several successful product hops by manufacturers of HIV medications, including Gilead.

86. *Id.* at 416.

87. *Id.* at 417.

88. Rachel Teitelbaum & Mark Cohen, *Obviousness, Hindsight, and Perspective: The Impact of* KSR v. Teleflex *on Biotech and Pharmaceutical Patents*, 25 NATURE BIOTECHNOLOGY 1105, 1106 (2007) (raising concern that the case and its progeny could "significantly negatively affect a multitude of biotech and pharmaceutical patents and heavily impact commercialization and patent protection in these arenas.").

89. Taiyin Yang, Reza Oliyai & Kenneth M. Kent, *The Making of the One Pill—Developing Single Tablet Regimens for HIV and for HCV*, 27 ANTIVIRAL THERAPY 1, 1 (2022).

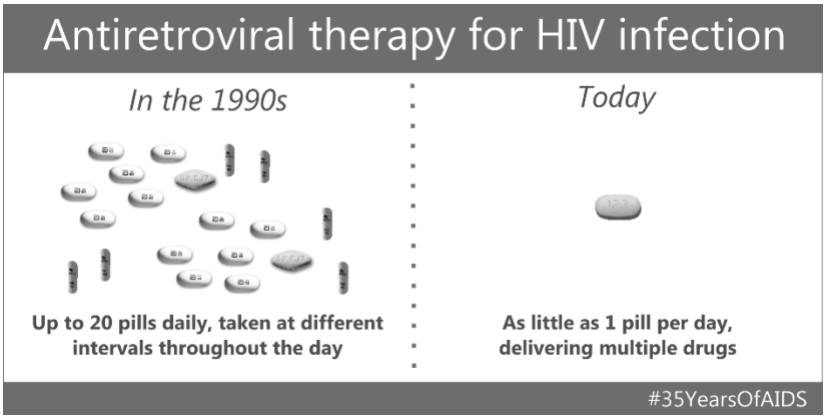

Figure 4:[90] A 2016 advertisement from NIAID promoting the advancement of single-pill antiretroviral drug combinations

Tahir Amin and Aaron S. Kesselheim looked at patent portfolios for two HIV drugs, ritonavir [Norvir] and lopinavir/ritonavir [Kaletra], identifying 108 patents held by Abbott Laboratories that could extend market exclusivity by 12 years.[91] Of these 108 patents, 49 pertained to composition and formulation of the drugs, including 7 patents covering combinations of ritonavir and/or lopinavir with other compounds.[92]

Overpatenting plagues HIV drugs to this day: A July 2023 New York Times article noted that Gilead Sciences delayed the development of a new combination therapeutic for HIV containing tenofovir until shortly before existing patents on the drug expired, allowing it to switch patients to the new product and extend market exclusivity by fourteen years.[93] Gilead documents referred to the maneuver as its "patent extension strategy," allowing it to continue to command high prices for tenofovir-based drugs despite the fact that the patent on tenofovir expired in 2017.[94]

In fact, many HIV drugs continue to have relatively little competition because the brand manufacturer will just combine them with other, newer products, limiting the ability of generic manufacturers to compete, even if they are able to produce generic combination pills for older versions. Scholars have noted that

> The popularity of brand single tablet formulations has allowed, due to one or more of the components being patented, antiretroviral therapy per patient costs to be maintained at around

90. NIAID, *Antiretroviral Therapy for HIV Infection* (illustration) (June 2, 2016), https://www.flickr.com/photos/niaid/27423001115/ [perma.cc/R3DX-LKXL].

91. Tahir Amin & Aaron S. Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study of How Patents on Two HIV Drugs Could Be Extended for Decades*, 31 HEALTH AFFS. 2286, 2286 (2012).

92. *Id.* at 2289 (Exhibit 1).

93. Rebecca Robbins & Sheryl Gay Stolberg, *How a Drugmaker Profited by Slow-Walking a Promising H.I.V. Therapy*, N.Y. TIMES (July 22, 2023), https://www.nytimes.com/2023/07/22/business/gilead-hiv-drug-tenofovir.html [perma.cc/9TAW-HG7H].

94. *Id.*

> the same level for many years, and as a result the benefits of reduced generic drug costs have become stalled for most payers.[95]

Desimplification of the HIV regimen—through replacement of a single tablet formulation by its branded and generic component drugs—increased pill burden but decreased costs substantially.[96] Despite these potential cost savings to payers and patients, the single-pill model for treating HIV continues with little opposition.

Patents for combination HIV medications should be regarded as "obvious to combine," given that treatment protocols and guidelines require a combination of medicines of certain classes to be co-administered for the treatment of the condition.[97]

2. Combination Medications: Duexis

For some commonly used medications, side effects complicate use for certain patients. As an example, non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen [Advil] can lead to gastrointestinal bleeding in some patients.[98] For that reason, physicians often recommend that higher risk patients take gastric acid-reducing medications like H2 blockers (e.g., famotidine [Pepcid]) or proton pump inhibitors (PPIs) (e.g., omeprazole [Prilosec] and esomeprazole [Nexium]) in conjunction with NSAIDs to decrease the risk of gastric bleeding and ulceration.[99] The medication Duexis contains 800 mg of ibuprofen and 26.6 mg of famotidine. Each of these medications is available as a generic and could be taken separately, but Horizon Therapeutics markets the combination medication to physicians with considerable success. According to one study, Duexis was covered by Medicare at $20.26 per pill when the price of the generic components was $0.28.[100] The drug contains 26.6 mg of famotidine, though the original strength of Pepcid was 20 mg when it was on patent.[101]

Perhaps the most egregious aspect of Medicare paying over $20 per pill for the prescription medication Duexis—a total of nearly $24 million for 6,000 patients in 2016—is that the component drugs are readily available for purchase over-the-

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95. Hartmut Krentz, Shayna Campbell & John Gill, *Desimplification of Single Tablet Antiretroviral (ART) Regimens–A Practical Cost-Saving Strategy?*, 18 J. INT'L ASS'N PROVIDERS AIDS CARE 1 (2019).

96. Rochelle P. Walensky, Paul E. Sax, Yoriko M. Nakamura, Milton C. Weinstein, Pamela P. Pei, Kenneth A. Freedberg, A. David Paltiel & Bruce R. Schackman, *Economic Savings Versus Health Losses: The Cost-effectiveness of Generic Antiretroviral Therapy in the United States*, 158 ANNALS INTERNAL MED. 84, 84 (2013).

97. *Ecolab, Inc. v. FMC Corp.,* 569 F.3d 1335, 1350 (2009) ("The question then is whether it would have been obvious to combine [Component 1] disclosed in [Patent 1] with [Component 2] disclosed in [Patent 2]. The answer is yes.").

98. Common NSAIDs include aspirin, ibuprofen, and naproxen.

99. *See* Anne Tuskey & David Peura, *The Use of H2 Antagonists in Treating and Preventing NSAID-induced Mucosal Damage*, 15 ARTHRITIS RES. & THERAPY S6, S11 (2013) ("[H2 receptor antagonists] are generally safe agents and, when given in high dose, are effective for the prevention of upper GI ulcers and dyspepsia in chronic NSAID users.").

100. Chana A. Sacks, ChangWon C. Lee, Aaron S. Kesselheim & Jerry Avorn, *Medicare Spending on Brand-name Combination Medications vs Their Generic Constituents*, 320 JAMA 650, 654 (2018) (see Table 2).

101. Of note, the additional 6.6 mg of famotidine likely does not offer significant additional clinical benefit but could limit efforts to desimplify Duexis into its constituent parts.

counter at any pharmacy. The list price for Duexis increased by 1,160% from 2011 to 2016.[102]

Commercial success is one of the *Graham* "secondary characteristics," yet the Duexis example suggests it may not be well-suited for nonobviousness determinations of pharmaceutical patents. Indeed, this may be a case of commercial success unmerited by the invention itself, since in most sectors, market forces might drive a costly product like Duexis off the market. Commercial success in the pharmaceutical industry, however, is largely driven by non-market forces that include detailing (pharmaceutical promotion) to physicians and other prescribers and direct-to-consumer advertising to patients.[103] In particular, government payers like Medicare are required to cover some drugs, no matter the list price. It would be difficult, then, to use commercial success as a consideration for nonobviousness when compelled purchases are involved. Ultimately, physicians who are fully informed about the cost of Duexis compared to generic famotidine and ibuprofen would be very unlikely to prescribe the medication to most patients.

3. Obviousness of Enantiomers

One of the more notable forms of product hopping comes via enantiomers of previously marketed drugs.[104] Two U.S. Court of Customs and Patent Appeals (CCPA) cases are relevant here.[105] The first, *In re Williams*, was decided in 1948, and held that the single enantiomer patent was nonobvious because it was not clear that the compound was a racemic mixture, and therefore, no one skilled in the art would be motivated to separate the mixture into component enantiomers.[106] *In re Adamson* was decided in 1960, and held that if a compound contains specific structures (namely, an asymmetric carbon atom), the PHOSITA would recognize this as a racemic mixture even if prior art references do not explicitly note this detail.[107]

Indeed, Darrow notes that later courts followed this line of reasoning with regard to the unpatentability of enantiomers as obvious over the prior art.[108] Yet as

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102. Sacks, *supra* note 100, at 653 (see Table 1).

103. *See generally* Lisa M. Schwartz & Steven Woloshin, *Medical Marketing in the United States, 1997-2016*, 321 JAMA 80, 80 (2019); *see also* Michael S. Sinha, Aaron S. Kesselheim & Jonathan J. Darrow, *Pharmaceutical Advertising in Medical Journals: Revisiting a Long-Standing Relationship*, 153 CHEST 9, 9 (2018).

104. *See supra* Section II.A.

105. Darrow, *supra* note 54, at 4–6.

106. *In re* Williams, 171 F.2d 319, 320 (C.C.P.A. 1948) ("[T]he idea of resolving [the racemic mixture] . . . would not occur to one skilled in the art."); *see also* Miles J. Sweet, *The Patentability of Chiral Drugs Post-*KSR*: The More Things Change, the More They Stay the Same*, 24 BERKELEY TECH. L.J. 129, 135–36 (2009).

107. *In re* Adamson, 275 F.2d 952, 954 (C.C.P.A. 1960) ("[O]ne of ordinary skill in the stereoisomer and pharmaceutical arts would recognize that the Adamson compounds exist as racemates . . . ."); *see also* Rebecca A. Eisenberg, *Pharma's Nonobviousness Problem*, 12 LEWIS & CLARK L. REV. 375, 425 (2008).

108. Darrow, *supra* note 54. *See* Brenner v. Ladd, 247 F. Supp. 51, 56 (D.D.C. 1965) ("[I]n the absence of unexpected or unobvious beneficial properties, an optically active isomer [i.e., an enantiomer] is unpatentable over either the isomer of opposite rotation or, as in this case, the racemic compound itself."); *see also In re* Anthony, 414 F. 2d 1383, 1386 (C.C.P.A. 1969) ("[U]nder existing law a stereoisomer is not patentable over its known racemic mixture unless it possesses unexpected properties not possessed by the racemic mixture.").

recently as 2007, the Federal Circuit upheld an enantiomer patent as nonobvious, noting that the PHOSITA "would generally have been motivated to develop new compounds rather than undertake the difficult and unpredictable task of resolving a known racemate" and "would have had no reasonable expectation of success."[109] After the successful marketing of several enantiomer drugs, later cases acknowledge that separation of racemic mixtures and studies of enantiomers are not only common practice in pharmaceutical research and development but can also be quite lucrative as follow-on products that can be used to product hop and extend the profitability of blockbuster drugs.[110]

A 2017 article by Mark Lemley notes that two important patent law doctrines collide when it comes to enantiomers: "obvious to try" and "unexpected results."[111] Lemley argues that "denying patents to enantiomers or biotechnological inventions that are obvious to try should not worry us unduly as a policy matter."[112] In the case of omeprazole (discussed *supra* Section IV.A.), there were arguably no unexpected results: Esomeprazole has a slightly higher efficacy as compared to omeprazole, but taking the racemic mixture omeprazole does not translate to lower safety or poorer clinical outcomes when taken at comparable doses.[113]

The dissolution of a racemic mixture into its component enantiomers should therefore be considered "obvious to try" by the USPTO if the mixture itself has been characterized either in a patent or in other prior art, including the scientific literature.[114] We should not incentivize manufacturers to strategically delay characterization of enantiomers from a racemic mixture in order to identify molecular targets for product life cycle management strategies, including product hops. We might, however, reward manufacturers for truly unexpected results, such

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109. Forest Labs., Inc. v. Ivax Pharm., Inc., 501 F.3d 1263, 1267 (Fed. Cir. 2007) (upholding patent on the enantiomer drug escitalopram [Lexapro], manufactured by Forest Labs).

110. Enantiomers of blockbuster drugs would be logical targets for drug development given the widespread prevalence and use of such compounds across the industry, so a follow-on enantiomer patent could be rejected as an obviousness-type double patent. *See* UCB, Inc. v. Accord Healthcare, Inc., 890 F.3d 1313, 1323 (Fed. Cir. 2018) ("In chemical cases, the double patenting inquiry is not whether a person of ordinary skill in the art would select the earlier compound as a lead compound, but rather whether the later compound would have been an obvious or anticipated modification of the earlier compound."); *see also* Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F. 3d 1293, 1301 ("[I]f it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a [PHOSITA] with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.").

111. Mark A. Lemley, *Expecting the Unexpected*, 92 NOTRE DAME L. REV. 1369, 1370 (2017).

112. *Id.* at 1392; *see also id.* at 1394 ("It is better to encourage pharmaceutical companies to identify the enantiomer that has the therapeutic benefit at the outset, rather than giving them extra patent life in exchange for waiting to do what was obvious for them to try.").

113. *See* Joel E. Richter, Peter J. Kahrilas, John Johanson, Paul Maton, Jeffrey Breiter, Clara Hwang, Victoria Marino, Bernard Hamelin & Jeffrey G. Levine, *Efficacy and Safety of Esomeprazole Compared with Omeprazole in GERD Patients with Erosive Esophagitis: A Randomized Controlled Trial*, 96 AM. J. GASTROENTEROLOGY 656, 656 (2001).

114. Advances have been made to make the chiral resolution of racemic mixtures into enantiomers and the synthesis of stereoisomers more efficient and cost-effective. *See generally* Michal Rachwalski, Niek Vermue & Floris P.J.T. Rutjes, *Recent Advances in Enzymatic and Chemical Deracemization of Racemic Compounds*, 42 CHEM. SOC. REV. 9268, 9268 (2013); *see also* Na Xu, Jun Zhu, Yin-Qi Wu, Yan Zhang, Jian-Ye Xia, Qian Zhao, Guo-Qiang Lin, Hui-Lei Yu & Jian-He Xu, *Enzymatic Preparation of the Chiral (S)-Sulfoxide Drug Esomeprazole at Pilot-Scale Levels*, 24 ORGANIC PROCESS RSCH. & DEV. 1124, 1124 (2020).

as a patent on an enantiomer that was significantly more efficacious or had other beneficial attributes (e.g., a better safety profile) as compared to its predecessor.

4. Nonobviousness of Other Secondary Patents

Price and Rai point out that some innovations in manufacturing should be unpatentable as obvious.[115] They point out that innovating dosage forms, methods of treatment, and methods of manufacture may be noble and add some societal value, but "the size of the reward fails to match the size of the innovation."[116]

The best way for USPTO to operationalize this would be to envision a PHOSITA with more comprehensive information at their disposal, particularly when a given product has a portfolio of patents covering it. Because the FDA's Orange Book—and soon, Purple Book—contain lists of these patents, greater collaboration would allow the USPTO (and courts) to more readily identify relevant prior art to make the determination of nonobviousness. If the FDA can supplement the patent examiner's prior art search, more drug patents may be deemed obvious over the prior art.

C. The Specificity of Nonobviousness

In one of its first efforts to reconcile its biomedical nonobviousness precedent with the Supreme Court's 2007 decision in *KSR v. Teleflex*, the Federal Circuit decided *In re Kubin* in 2009. The court held that a patent application fails for obviousness when a particular chemical structure would be "obvious to try with a reasonable expectation of success."[117] The Federal Circuit in *Kubin* rejected its prior holding in *In re Deuel*, a 1995 decision which imposed the stringent requirement that in order to establish obviousness, "[t]here must . . . be prior art that suggests the claimed compound."[118] *Kubin* also stood for the principle that the PHOSITA's skill level is not static and advances over time.[119]

Other limitations discussed in *KSR*—predictable results and upgrades—may also serve to limit nonobviousness in patents for pharmaceuticals. In fact, the in-house enterprise of product life cycle management depends on experts like pharmaceutical chemists mapping out the future trajectory of a product line,

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115. Price and Rai, *supra* note 69, at 863.

116. *Id.* ("[I]nnovation in manufacturing biologics should have the same sort of reward innovation found in manufacturing other goods: it should allow drugmakers to compete by making their products more efficiently, or with higher quality. Patents (or secrecy) can protect that competitive advantage, creating incentives for just that sort of innovation. However, in the current system, patents on those innovations can instead be used to game the system and prevent competition altogether.").

117. *See* Thomas A. Isenbarger, Note, *In Re* Kubin's *Reinvigorated Nonobviousness Standard for DNA Patents*, 6 WIS. L. REV. 1435, 1448 (2009) (noting that the Federal Circuit in *Kubin* restored its own analysis from *In re O'Farrell* (Fed. Cir. 1988): obviousness is appropriate when prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention," and "a reasonable expectation of success." *In re* Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009)). Notably, *In re Kubin* was decided before the landmark 2013 Supreme Court decision in *Association for Molecular Pathology v. Myriad Genetics*.

118. *In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

119. Isenbarger, *supra* note 117, at 1465; *see also* Rebecca Hays, Note, *Biotechnology Obviousness in the Post-Genomic Era:* KSR v. Teleflex *and In re* Kubin, 10 MINN. J. L. SCI. TECH. 801, 829 (2009) ("Standards implemented by the Federal Circuit in the industry's infancy are coming under increased scrutiny and have perhaps been outgrown by advances in the art."); *see also* Joanne Kwan, *A Nail in the Coffin for Gene Patents*, 25 BERKELEY TECH. L.J. 9, 9 (2010).

including the secondary chemical structures that may eventually result in product hops. Manufacturers will often detail their plans to shareholders in rather transparent ways: U.S. Securities and Exchange Commission filings (10-K filings) and annual reports may disclose patent expirations, express concern about windfalls from generic competition, or detail plans to protect market share.[120]

D. Who is the PHOSITA?

In the world of pharmaceutical patenting, the USPTO should also reconsider who the PHOSITA is for purposes of nonobviousness. *In re Kubin* offered a vision of an evolving PHOSITA whose knowledge base advances with scientific progress. Yet the outcome of an obviousness determination hinges on exactly what the PHOSITA knows. With that said, how much knowledge should the PHOSITA possess?

Darrow suggests that the PHOSITA "is presumed to have read, understood, and remembered every existing reference from the prior art."[121] He argues that proper selection of the PHOSITA is paramount: "While two individuals might be working in the same field or art, the particular role each plays may result in vastly different perspectives from which to judge obviousness."[122] Applied to pharmaceuticals, perhaps the PHOSITA should be a pharmaceutical chemist, who may have a better understanding of how to synthesize an extended-release formulation of a given drug or how to perform a high-yield chiral extraction of an enantiomer from a racemic mixture.

Or perhaps the better standard is that of a practicing physician in a particular specialty who understands what drugs ought to exist as combination pills. A primary care physician, for instance, may have already recommended that patients take famotidine with NSAIDs to reduce their risk of upper GI bleeding prior to the patenting of Duexis, rendering the combination obvious to the physician-PHOSITA.[123] That physician may also be skeptical of the need for differential dosing of famotidine: 26.6 mg/pill in Duexis compared to 20 mg/pill in generic famotidine.[124] Under *KSR*, predictable combinations are suspect;[125] depending on the PHOSITA, a strong case may be made under *KSR* that the combination of ibuprofen and famotidine is predictable. In addition, the holding in *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, when applied in the context of combination medications,

120. In one clear example, Johnson & Johnson revealed its "focused biosimilar readiness plan" to shareholders, a plan to delay Pfizer's launch of a biosimilar for its blockbuster biologic infliximab [Remicade]. *See* Arlene Weintraub, *Stay Calm, Investors. J&J Has a 'Readiness Plan' in Place for Remicade Biosim Launch*, FIERCE PHARMA (Oct. 18, 2016, 10:13 AM), https://www.fiercepharma.com/pharma/j-j-drug-sales-soar-q3-but-remicade-biosimilar-looms [perma.cc/GHU6-DEZ7].

121. Jonathan J. Darrow, *The Neglected Dimension of Patent Law's PHOSITA Standard*, 23 HARV. J. L. TECH. 227, 235 (2009).

122. *Id.* at 238.

123. *See* R.S.B. Ehsanullah, M.C. Page, G. Tildesley & J.R. Wood, *Prevention of Gastroduodenal Damage Induced by Non-Steroidal Anti-Inflammatory Drugs: Controlled Trial Of Ranitidine*, 297 BRITISH MED. J. 1017, 1017 (1988) (Note: ranitidine [Zantac] is in the same class of drugs as famotidine.).

124. Interestingly, Horizon's patent on the combination drug (U.S. Patent No. 8,501,228) describes dosing of famotidine between 24 and 28 mg, without clear reasoning for the slight increase in dose compared to generic 20 mg famotidine tablets.

125. However, the combination is described as "chemically incompatible" in the background, which may imply that the drugs had less reason to be combined under a *KSR* analysis.

may point to obviousness since the component drugs and scientific principle (of combining them) would be obvious to a skilled artisan.[126]

In a piece titled "*People Having Ordinary Skills in the Arts*," Dan Traficonte and Ben Armstrong note that "what is obvious to a team of people with varied expertise is often not obvious to a single person, even one of extraordinary skill."[127] They instead suggest a switch to a Team Having Ordinary Skill in the Arts (THOSITA), which "establishes the unit of analysis in patent law as (a) a team of individuals, of (b) a size consistent with teams inventing similar technologies, and (c) representing ordinary skills commonly found in the invention of related technologies."[128]

Given the wide breadth of knowledge required to understand many modern-day inventions, one thing is for certain: the USPTO would benefit from more input from stakeholders like the FDA when making obviousness determinations. Manufacturers should feel free to develop such products if they believe they are worth marketing, but they should not get additional patent protection for those incremental innovations if they are obvious in light of the prior art.[129] A sophisticated pharmaceutical PHOSITA standard may also require more expert witnesses at trial, which could pose problems of adversarial bias while presenting a paradox between expert witnesses and the lay juries and judges that decide patent cases.[130]

Post-*KSR*, we are left with a nonobviousness standard that some scholars believe is indeterminate; with the level of ordinary skill undefined, "the Supreme Court . . . [often] substitute[s] its lay technological judgment for that of a person of ordinary skill."[131] Laura Pedraza-Fariña and Ryan Whalen highlight the challenges in defining the skilled artisan as follows: "The PHOSITA's dual nature as a *legal* construct reflecting normative policy goals, and an *empirical* construct reflecting real-world practices, complicates the judicial task of articulating a clear test for determining the PHOSITA's perspective in each relevant doctrine."[132]

The better approach here is to bring more sophistication to the pharmaceutical PHOSITA. Perhaps Daralyn Durie and Mark Lemley's characterization of the

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126. Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948) ("The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men."); *see* S. Sean Tu, *Funk Brothers—An Exercise in Obviousness*, 80 UMKC L. REV. 637, 637 (2012) ("[T]his article argues that *Funk Brothers* is erroneously relied upon by judges and juries alike to determine the limits of patentable subject matter, and that in reality, *Funk Brothers* is a case that outlines the obviousness standard."). *But see* Oskar Liivak, *Don't Cite Funk*, 72 CATH. U. L. REV. 193, 206 (2023) ("[E]ven as an obviousness case, Funk is highly questionable as it relied upon the one case that was explicitly overruled by the 1952 Patent Act.").

127. Dan Traficonte & Ben Armstrong, *People Having Ordinary Skills in the Arts*, 37 HARV. J. L. & TECH 329, 329 (2024).

128. *Id.* at 329–330.

129. Ryan Abbott, *Everything Is Obvious*, 66 UCLA L. REV. 2, 10 (2019) ("Patents are not intended to be granted for incremental inventions. Only inventions which represent a significant advance over existing technology should receive protection.").

130. Greg Reilly, *Rethinking the PHOSITA in Patent Litigation*, 48 LOY. U. CHI. L.J. 501, 518–520 (2016) ("The result is that instead of evaluating expert testimony on its merits or substance, lay judges and juries are left to rely on secondary criteria like demeanor, credentials, and superficial explanatory plausibility." *Id.* at 520).

131. Gregory Mandel, *The Non-Obvious Problem: How the Indeterminate Nonobviousness Standard Produces Excessive Patent Grants*, 42 U.C. DAVIS L. REV. 57, 71 (2008).

132. Laura Pedraza-Fariña & Ryan Whalen, *The Ghost in the Patent System: An Empirical Study of Patent Law's Elusive "Skilled Artisan,"* 108 IOWA L. REV. 247, 258 (2022) (emphasis in original).

PHOSITA's work fits best: "[N]ot isolated in an office with prior art hanging from the walls, but in collaborative teams with an open exchange of ideas."[133] The most appropriate collaborative team to work with USPTO on the obviousness of pharmaceutical patents may be the FDA—the call for greater USPTO-FDA collaboration provides an excellent opportunity to do just that.[134]

V. UTILITY

Utility is often an afterthought in patentability. In 1817, Justice Story famously remarked that "[t]he law . . . does not look to the degree of utility."[135] The famous treatise, The Law of Patents, similarly noted that "[w]hen actual utility exists, its degree is unimportant."[136] As Justice Story noted in a separate case, "[a]ll that the law requires is, that the invention should not be frivolous or injurious to the well-being, good policy, or sound morals of society," pointing out that "[w]hether it be more or less useful is a circumstance very material to the interests of the patentee, but of no importance to the public."[137] More recently, in its 1999 decision *Juicy Whip, Inc. v. Orange Bang, Inc.*, the Federal Circuit reiterated that "[t]he threshold of utility is not high: An invention is 'useful' . . . if it is capable of providing some identifiable benefit."[138]

A. Utility: A Higher Bar for Pharmaceuticals?

In *Patently Impossible*, Sean B. Seymore argues that utility has historically been a high bar for pharmaceuticals.[139] Seymore points to two CCPA cases, the first a 1963 case in which Judge Giles Rich expressed considerable skepticism regarding patents for compounds that claimed to treat cancer. By 1980, the CCPA changed its tune, noting that the effective treatment of cancer was no longer "impossible."[140] In both cases, the burden of proof was on the inventor to demonstrate utility.[141]

By 1995, *In re Brana* was decided by the CCPA's successor court, the Federal Circuit, shifting the modern patent utility doctrine in favor of patentees.[142] Importantly, the burden of proof for utility shifted to the USPTO, with the court asserting that research and development should not be stifled by an overly rigid interpretation of utility.[143] Yet a decade later, the Federal Circuit decided *In re Fisher* in 2005, requiring that a patentee demonstrate both substantial utility ("a significant and presently available benefit") and specific utility ("a well-defined and particular

133. Daralyn J. Durie & Mark A. Lemley, *A Realistic Approach to the Obviousness of Inventions*, 50 WM. & MARY L. REV. 989, 1003 (2008).

134. *See USPTO—FDA Collaboration Initiatives*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/initiatives/fda-collaboration [perma.cc/MN4G-A4XM] (last visited Oct. 17, 2024).

135. Bedford v. Hunt, 3 F. Cas. 37, 38 (C.C.D. Mass. 1817) (No. 1,217).

136. WILLIAM C. ROBINSON, THE LAW OF PATENTS FOR USEFUL INVENTIONS (1890).

137. Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568).

138. Juicy Whip, Inc. v. Orange Bang, Inc., 185 F.3d 1364, 1366 (Fed. Cir. 1999).

139. Sean B. Seymore, *Patently Impossible*, 64 VAND. L. REV. 1491 (2011).

140. *Id.* at 1518–1521 (citing two key U.S. Court of Customs and Patent Appeals cases, *In re Citron*, 325 F.2d 248 (C.C.P.A. 1963) and *In re Jolles*, 628 F.2d 1322 (C.C.P.A. 1980)).

141. *Id.*

142. *Id.* at 1521.

143. *Id.* at 1521–1522 (citing Rebecca S. Eisenberg, *Analyze This: A Law and Economics Agenda for the Patent System*, 53 VAND. L. REV. 2081, 2086 (2000)).

benefit to the public").[144] The court remarked, "Fisher's alleged uses are so general as to be meaningless."[145]

1. Prodrugs: Gabapentinoids

Consider the drugs gabapentin [Neurontin] and pregabalin [Lyrica]. Gabapentin was approved in 1993 as a treatment for neuropathic pain, including pain from peripheral neuropathy, diabetic neuropathy, and post-shingles neuropathy.[146] In 2004, the company developed the prodrug pregabalin [Lyrica], which has better gastrointestinal absorption compared to gabapentin. A second prodrug, gabapentin enacarbil [Horizant], was more recently developed as an extended-release formulation. For each of these prodrugs, the incremental innovations do not provide sufficient utility to warrant new patents. In fact, a recent review of gabapentinoid efficacy demonstrated only modest pain benefits for patients—a sharp contrast to the extent to which these drugs are used in clinical practice.[147] Excess spending on the prodrugs Lyrica and Horizant would have been better spent funding research and development into pain therapeutics with novel mechanisms of action, an area that has historically lagged in research support.[148] Instead, as of January 2018, Pfizer (the manufacturer of Lyrica) conducted 238 trials of the drug for nonapproved indications in an effort to expand the market for its blockbuster drug.[149]

2. Prodrugs: Cures for Hepatitis C

In contrast, consider a prodrug like sofosbuvir [Sovaldi], Gilead's landmark curative therapy for hepatitis C. In patent infringement litigation against Gilead Sciences, Merck described Sovaldi as a prodrug that would be converted into three different compounds upon enzymatic conversion in the hepatocyte (liver cell).[150]

Sofosbuvir transformed the treatment of hepatitis C by doing something earlier therapeutics could not: limit its effect to hepatocytes, thereby eliminating the systemic and often toxic effects of previous regimens. Not only did this mitigate the adverse effects associated with treating hepatitis C, but it also shortened the duration of therapy and maximized efficacy to 95% in its pivotal trial.[151] Much of

144. *In re* Fisher, 421 F.3d 1365, 1366 (Fed. Cir. 2005).

145. *Id.* at 1370; *see also In Re* Kirk, 376 F.2d 936, 942 (C.C.P.A. 1967) ("It cannot be presumed that a steroid chemical compound is 'useful' . . . or that one of skill in the art will know 'how to use' it, simply because the compound is closely related only in a structural sense to other steroid compounds known to be useful.").

146. CTR. FOR DRUG EVALUATION AND RSCH., NEW DRUG APPLICATION 20-235/S-015 (1999).

147. C.D. Williams, Z. Al-Jammali & M.C. Herink, *Gabapentinoids for Pain: A Review of Published Comparative Effectiveness Trials and Data Submitted to the FDA for Approval*, 83 DRUGS 37 (2023).

148. Thomas J. Hwang, Michael S. Sinha, Chintan V. Dave & Aaron S. Kesselheim, *Prescription Opioid Epidemic and Trends in the Clinical Development of New Pain Medications*, 94 MAYO CLINIC PROC. 2437, 2437 (2019); *see also* Kelly K. Dineen Gillespie & Michael S. Sinha, *Realigning Incentives for Novel Pain Therapeutics*, 137 ANESTHESIOLOGY 134, 134 (2022).

149. Federico, *supra* note 43.

150. Gilead Sciences, Inc. v. Merck & Co, Inc., No. 13-CV-04057-BLF, 2015 WL 2062575 (N.D. Cal. May 1, 2015).

151. Press Release, Gilead Sciences, Inc., Gilead's Sovaldi Demonstrates Efficacy and Safety Among Chronic Hepatitis C Patients with Advanced Liver Disease (Apr. 11, 2014), https://www.gilea

this clinical success can thus be attributed to the development of sofosbuvir as a prodrug. Because the drug is intended to exert its effect in the liver, this form of prodrug may have more plausible utility due to its specificity.

3. Reformulations: Citrate-Free Adalimumab [Humira]

Humira is the highest-grossing pharmaceutical product of all-time. As biosimilars sought to enter this lucrative market and compete with Humira, AbbVie launched a citrate-free formulation of its injectable biologic in 2018.[152] On its website, AbbVie highlights that the new product reduces pain immediately following injection via the removal of the citrate buffer, a reduced injection volume, and a thinner needle.[153]

Though less painful daily injections offer tangible benefit to patients, it also comes at the price of maintaining market monopolies and extending profit margins for AbbVie. Indeed, Medicaid prescriptions for Humira Citrate-free increased substantially after its market launch, representing 85% of all adalimumab prescriptions by 2021. Medicaid spent approximately $4.4 billion more from 2018-2021 due to substantially lower statutory rebates for Humira Citrate-free as compared to Humira.[154]

Given this successful product hop to Humira Citrate-free, some expressed concern that biosimilars for non-citrate-free Humira might not be able to compete with AbbVie's soft switch to Humira Citrate-free.[155] Fortunately, that question was resolved when the FDA approved several high-concentration and citrate-free versions of adalimumab biosimilars, which enables them to compete more meaningfully for market share against Humira Citrate-free.[156]

Arguably, the added utility of citrate removal did not warrant billions of dollars in excess spending by switching most Humira users over to the costlier Citrate-free version. Though purportedly developed for patient benefit, the real windfall came through the successful product hop to Humira Citrate-free and the effort to thwart biosimilar competition.[157] The path to increased competition was aided by a citizen

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d.com/news-and-press/press-room/press-releases/2014/4/gileads-sovaldi-demonstrates-efficacy-and-safety-among-chronic-hepatitis-c-patients-with-advanced-liver-disease [perma.cc/F2NX-WMU3].

152. Sinha, *supra* note 14, at 337–40.

153. *Id.* at 339; *see Humira*, HUMIRA, https://www.humira.com/citrate-free [perma.cc/2LMD-6TX9] (last visited Jan. 18, 2025).

154. Junyi Wang, ChangWon C. Lee, Aaron S. Kesselheim & Benjamin N. Rome, *Estimated Medicaid Spending on Original and Citrate-Free Adalimumab From 2014 Through 2021*, 183 JAMA INTERNAL MED. 275, 276 (2023).

155. Zachary Brennan, *Boehringer Nabs FDA's First Interchangeability Designation for its Humira Competitor – But Will It Matter?*, ENDPOINTS NEWS (Oct. 18, 2021, 4:19 PM), https://endpts.com/boehringer-nabs-fdas-first-interchangeability-designation-for-its-humira-competitor-but-will-it-matter/ [perma.cc/9S94-VCG4]; *see also* Sinha, *supra* note 14, at 337–340.

156. Brian Park, *Several Biosimilars to Humira Now Available, Including an Interchangeable Product*, MED. PROS. REFERENCE (July 5, 2023), https://www.empr.com/home/news/several-biosimilars-to-humira-now-available-including-an-interchangeable-product [perma.cc/9AZ7-WY87].

157. AbbVie may have been hoping that biosimilar manufacturers would not be able to introduce citrate-free versions or to double-concentrate their formulas given that Humira Citrate Free is a different product than the original Humira formulation. *See* Brennan, *supra* note 155.

petition from Boehringer-Ingelheim, which paved the way for the FDA approval of more concentrated biosimilars.[158]

D. Modified Dosage Regimens: Glatiramer Acetate [Copaxone]

The injectable drug Copaxone was first approved in 2002 to treat multiple sclerosis.[159] As its market exclusivity period wound down in 2015, its manufacturer, Teva Pharmaceuticals, introduced a new formulation of the drug with a reduced dosing regimen.[160] The reformulated product was twice as concentrated as its predecessor but could be injected only three times a week rather than daily.[161] As patients switched from daily Copaxone to three-times-weekly Copaxone, excess national health care spending of between $4.3 billion and $6.5 billion occurred in spite of the availability of daily generic glatiramer acetate at significantly lower cost.[162] Brand name spending decreased only upon the introduction of a three-times-weekly generic version of glatiramer acetate.[163]

The question here, as with Humira, is whether these incremental improvements to Copaxone, which provide small but difficult-to-quantify benefits to patients, warrant billions of dollars in excess spending.[164] The patenting of new dosages and dosing schedules can delay the market penetration of generics, but are those improvements clinically useful? What amount of excess spending for incremental innovations gets us to the point that the innovation should be deemed unpatentable as "injurious to the well-being, good policy, or sound morals of society?"[165] Even if patent examiners at the USPTO do not have the expertise to make this determination, consultation with the FDA would likely yield these insights. This could undermine the patentability of the new product, thereby mitigating efforts to product hop in this manner.

B. Strengthening the Utility Standard?

The utility standard is arguably the lowest hurdle on the road to patentability—it may not even be a hurdle at all.[166] Absent a few notable instances, it is hardly ever

158. BOEHRINGER INGELHEIM, CITIZEN PETITION REQUESTING THE FOOD AND DRUG ADMINISTRATION TO MAKE STRENGTH DETERMINATIONS FOR PARENTERAL BIOLOGICS BASED UPON THE TOTAL DRUG CONTENT OF THE CONTAINER WITHOUT REGARD TO CONCENTRATION (2020), https://www.boehringer-ingelheim.com/us/bipdf/boehringer-ingelheim-bpcia-strength-citizen-petition [perma.cc/V4TH-86FX].

159. CTR. FOR DRUG EVALUATION AND RSCH., NEW DRUG APPLICATION 20-622/S-015 (2001).

160. Benjamin N. Rome, Frazer A. Tessema & Aaron S. Kesselheim, *US Spending Associated with Transition from Daily to 3-Times-Weekly Glatiramer Acetate*, 180 JAMA INTERNAL MED. 1165, 1165 (2020).

161. *Id.*

162. *Id.* at 1169.

163. *Id.*

164. Perhaps this is more of a payer problem than a patent problem. An insurance company could say "your new three times a week formulation is worth an extra $50 a month." That is beyond the scope of this piece. For now, list prices determine the costs of drugs, with payers like Medicare limited in its ability to decline coverage.

165. Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568).

166. Justice Story noted that "[t]he law . . . does not look to the degree of utility; it simply requires, that it shall be capable of use, and that the use is such as sound morals and policy do not discountenance or prohibit." Bedford v. Hunt, 3 F. Cas. 37, 37 (C.C.D. Mass. 1817) (No. 1,217).

raised during patent prosecution, much less in litigation.[167] But what if the patentee was required to describe, in the application, the anticipated clinical utility of a new formulation over existing therapies? This would admittedly represent a sea change in patent law, but with pharmaceutical patents becoming increasingly complex and incremental innovations rewarded with the same twenty-year-long patents as transformative ones, is it worth elevating utility to avoid outsized rewards?

Given that the manufacturer usually obtains secondary and tertiary patents after the flagship product is marketed, a clinical utility threshold might not be as unduly burdensome as it seems.[168] Of the aforementioned examples, sofosbuvir has more utility than pregabalin or gabapentin enacarbil. The patent system should have a mechanism for rewarding the former over the latter. But how might a strengthened utility requirement work?

In *Reinventing Usefulness*, Michael Risch argues for a direct commercial utility requirement.[169] Under this standard, there must be "sufficient evidence to convince a person with skill in the art that (a) there is a market for the invention, and that (b) the invention can be manufactured at a cost sufficient to fulfill market demand."[170] As a caveat, he notes that commercial utility would not be met "where there is evidence that near-term market demand can be satisfied."[171]

Even with the caveat, this standard may not be well suited for pharmaceutical patents. In most sectors, a useless product will not sell. After all, who wants to buy a mousetrap that doesn't work? Pharmaceuticals are inherently different. It's not that the new product (the product hop) does not work, but rather, that its incremental value over existing products would ordinarily lead an informed consumer to choose the cheaper alternative. Three factors complicate this choice for pharmaceuticals: (1) consumers are rarely the sole decisionmakers, (2) consumers do not usually bear the full costs, and (3) aggressive pharmaceutical marketing strategies can convince physicians to prescribe costly products with cheap alternatives (see Duexis, *supra* Section V.B.(2)).[172]

First, the decision to prescribe a medication has historically been one for physicians to make alone, but as patient autonomy and shared decision-making emerged as fundamental components of the physician-patient relationship, a meeting of the minds was necessary for a medication to be prescribed. More recently, other factors relating to insurance coverage, formularies, and reimbursement have complicated the process, in some cases removing the decision from physician and patient entirely.[173] Only in certain limited situations do

167. *See In re* Fisher, 421 F.3d 1365 (Fed. Cir. 2005) (asserting that to be patentable, claimed invention must have substantial and specific 'utility,' i.e., invention must have significant and presently available benefit to public, and its claimed use must not be so vague as to be meaningless); *see also* Newman v. Quigg, 877 F.2d 1575 (Fed. Cir. 1989) (claims to a perpetual motion machine ruled inoperable); *In re* Swartz, 232 F.3d 862 (Fed. Cir. 2000) (claims of utility and operability of cold fusion ruled inoperable).

168. To be fair, the FDA evaluates utility to some degree when it approves drugs. Meeting in the middle somewhere on utility standards could be a beneficial outcome of collaboration.

169. Michael Risch, *Reinventing Usefulness*, 2010 BYU L. REV. 1195, 1235 (2010).

170. *Id.* at 1240–1241.

171. *Id.* at 1241.

172. The clearest examples of this are enantiomer drugs.

173. An example of this could be the following: A patient and her physician want to initiate treatment of a particular medical condition with a new and costly medication. The patient's insurance company may have a formulary that requires the patient to try (and fail) an older, cheaper medication

consumers have full autonomy to make decisions about what products to purchase and take, including OTC drugs and dietary supplements. In each case, the consumer usually bears the full cost of those products even if pre-tax dollars are used.[174]

Instead of a utility requirement that hinges on commercial success, a better approach would be to acknowledge that commercial success may have little to do with the usefulness of a product hop. A 2021 Federal Circuit decision held that "evidence supporting objective indicia of nonobviousness must be shown to have a nexus to the claimed invention . . . [e]vidence of commercial success, therefore, can be linked to an inventive combination of known elements to show a sufficient nexus."[175] Indeed, prescribing of Duexis to Medicare patients was more likely driven by detailing to physicians, coupled with lower sensitivity to cost among patients with Part D supplemental insurance plans that reduce or eliminate copayments.[176] This may not matter if these arguments were not asserted during patent prosecution, but it offers USPTO and patent examiners the chance to raise these important utility-focused questions prior to patent issuance.

Other scholars question whether the current utility bar is really as low as it seems. Seymore raises concern in *Making Patents Useful* that the vague requirement of "substantial" and "specific" utility as articulated by the Supreme Court in *Brenner v. Manson* (and reiterated in *Fisher*) "could actually inhibit scientific progress."[177] He notes that "[u]tility in the chemical, pharmaceutical, and biotechnological arts now has nothing to do with the invention's inherent usefulness to a PHOSITA, ability to advance scientific knowledge, or potential to indirectly benefit the public. In these fields, the utility standard is nothing more than a subjective and arbitrary value judgment."[178]

I would argue the contrary—the pendulum has swung too far in the opposite direction—the utility standard has returned to the much-lower standard articulated by Justice Story in 1817.[179] The aforementioned examples (*supra* Section VI.A.3. and VI.A.4.) highlight that products with minimal utility over their predecessors are awarded patents that extend market exclusivity, generating billions of dollars in excess spending. Thus, when such a "subjective and arbitrary value judgment"[180] is so detrimental to society as to violate Justice Story's foundational principles of societal good derived from utility, that patent should be void for lack of utility.

For some secondary patent applications, USPTO could require a demonstration of utility based on comparison to available alternatives. That is, the

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prior to covering the newer, more expensive drug. There may be therapeutic advantages to these requirements, but the primary driver is cost.

174. For instance, a Flexible Spending Account allows an employed individual to allocate pre-tax dollars to be spent on copayments and other select products.

175. Chemours Co. FC, LLC v. Daikin Indus., Ltd., 4 F.4th 1370 (Fed. Cir. 2021); *see also* Robert P. Merges, *Commercial Success and Patent Standards: Economic Perspectives on Innovation*, 76 CALIF. L. REV. 803, 806 (citing concerns at the time that "the Federal Circuit . . . may actually be weakening [the patent system] by rewarding inventions that are commercially successful but that represent relatively minor technological advances.").

176. Indeed, detailing to physicians may include free samples for patients and copay coupons that reduce their out-of-pocket spend. *See generally* Schwartz & Woloshin, *supra* note 103.

177. Sean B. Seymore, *Making Patents Useful*, 98 MINN. L. REV. 1046, 1065 (2014); *see also* Brenner v. Manson, 383 U.S. 519 (1966).

178. Seymore, *supra* note 177, at 1066.

179. *See supra* Section VI.

180. Seymore, *supra* note 177, at 1066.

inventor might be expected to establish that the product has some measurable clinical utility as compared to the originator molecule, especially if that molecule is likely to be submitted to the FDA for approval as a new therapeutic. Again, this would represent a substantial departure from Justice Story's position in 1817 that "[w]hether [an invention] be more or less useful is a circumstance very material to the interests of the patentee, but of no importance to the public."[181] But with pharmaceutical prices so high that the President called on the USPTO and FDA to take action, revisiting this standard may not be unreasonable.

The USPTO could also enlist the FTC's assistance in assessing the anticompetitive motivations of the inventor or the corporate assignee in order to distinguish detrimental from beneficial in the context of product hops.[182] This could come from asking two simple questions: (1) what is the problem to be solved?, and (2) what is the purpose of the invention?

The FDA could be a valuable partner in making these determinations, as the clinical utility of new molecular entities (e.g., primary patents) may not be certain at the time of patenting but the clinical utility of secondary patents like salts or enantiomers would be. A 2021 study found that most single-enantiomer drugs did not offer an added safety or efficacy benefit, though there were some exceptions: 12.8% favored the enantiomer on efficacy end points, while 13.7% favored the single enantiomer on safety end points.[183] Manufacturers might be expected to point to some added safety or efficacy benefit to meet the clinical utility threshold for enantiomer patents.[184]

VI. WRITTEN DESCRIPTION AND ENABLEMENT

In the famous incandescent lamp patent case of 1895, Sawyer & Man's patent was invalidated for lack of enablement.[185] The court held that Sawyer & Man did not sufficiently describe the filament to enable someone skilled in the art to practice the invention, pointing to Thomas Edison's discovery of improved "high resistance" filaments that specifically used bamboo.[186] In rejecting Sawyer & Man's "genus claim" for all fibrous and textile materials, the Court held that the "species" of filamentous bamboo discovered by Edison had not been enabled by the Sawyer & Man patent.[187]

Modern enablement jurisprudence can be summed up by a 2004 Federal Circuit decision in *Chiron Corp. v. Genentech, Inc.*, which noted that enablement requires a certain degree of guidance or direction to the ordinary artisan: "Nascent technology . . . must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary

181. Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568).

182. FTC involvement in product hops is not new, nor is its interest in working with other federal agencies to stem anticompetitive conduct.

183. *See* Long et al., *supra* note 55.

184. For enantiomers, reassessment of nonobviousness may be the easier path, as it would not disrupt two centuries of precedent in patent utility. But that does not mean utility should be entirely off-limits in USPTO-FDA discussions, especially when it is such a low bar.

185. Consol. Elec. Light Co. v. McKeesport Light Co., 159 U.S. 465 (1895).

186. *Id.* at 468–69.

187. *Id.* at 472.

skill in the art has little or no knowledge independent from the patentee's instruction."[188]

What about the impact of broad claims in pharmaceutical development? In *The Death of the Genus Claim*, Dmitry Karshtedt, Mark A. Lemley, and Sean B. Seymore note that "genus claims appear in all areas of technology, [and] they are ubiquitous in chemistry, pharmaceuticals, and biotechnology."[189] As such, the protection of a broad genus claim provided meaningful protection for discoveries in these relatively unpredictable fields.[190] Yet the authors note that in the last thirty years, genus claims have invariably been struck down by the Federal Circuit, which they describe as "a puzzling and troubling doctrinal shift."[191]

A. The Modern Written Description

Two important cases addressing the status of the genus claim were decided in the last decade.[192] The Federal Circuit decided *Amgen, Inc. v. Sanofi* in 2017, holding that patents on a screening process used to select antibodies were not invalid due to lack of written description and enablement.[193] In order for the genus claim to satisfy the written description requirement, the patentee had to be "in possession of the claimed subject matter," which required Amgen to disclose "a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."[194] In 2021, the Federal Circuit decided *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, holding that claims were invalid for lack of written description.[195] The court held, "Simply put, the [patent] claims a 'problem to be solved while claiming all solutions to it . . . cover[ing] any compound later actually invented and determined to fall within the claim's functional boundaries,' which fails to satisfy the written description requirement."[196]

B. The Supreme Court Weighs In

Though both *Juno v. Kite* and *Amgen v. Sanofi* dealt with written description, the Court granted cert in the latter while denying it in the former. In fact, Juno submitted a petition for rehearing, pointing out that the "two cases involve the very same sentence of the very same statute, 35 U.S.C. §112(a)." Policymakers, including former Chief Judge of the Federal Circuit, Paul Michel, argued that "reversal in

188. Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254 (Fed. Cir. 2004).

189. Dmitry Karshtedt, Mark A. Lemley & Sean Seymore, *The Death of the Genus Claim*, 35 HARV. J. L. & TECH. 1, 13 (2021).

190. *Id.* at 25.

191. *Id.* at 4, 54.

192. Amgen Inc. v. Sanofi, 872 F.3d 1367, 1367 (Fed. Cir. 2017); Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1330 (Fed. Cir. 2021).

193. *Amgen Inc.*, 872 F.3d at 1367.

194. *Id.* at 1373 (citing Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1350 (Fed. Cir. 2010)).

195. *Juno Therapeutics, Inc.*, 10 F.4th at 1330.

196. *Id.* at 1339 (citing *Ariad*, 598 F.3d at 1353).

Amgen while allowing the Federal Circuit's precedent in the *Juno* decision to stand would lead to doctrinal chaos for Section 112 jurisprudence moving forward."[197]

In June 2023, the Supreme Court handed down its verdict in *Amgen v. Sanofi*, invalidating Amgen's genus claim for lack of enablement.[198] Consistent with Federal Circuit precedent, the Court noted that patents of chemical structures with potentially millions of different iterations (very few of which were enumerated in the patent itself) did not adequately disclose the nature of the invention as to enable someone skilled in the art to reproduce the invention.[199] An amicus brief supporting Amgen lamented that the Federal Circuit's shift to a "full-scope enablement standard" has "frustrate[d] patenting and innovation in the chemical and life sciences."[200] By contrast, an amicus brief supporting Sanofi argued that Amgen had only enabled a roadmap, "a broad research plan that teaches persons of skill to invent on their own."[201]

C. Written Description and Product Hops

Though the brief in support of Amgen cautions that invalidating genus claims would "discourage inventors from filing patent applications," the drive to patent in the pharmaceutical sector is stronger than ever.[202] Rather, the Supreme Court decision may limit product hopping by favoring earlier disclosure of the most promising compounds in patent applications, which could reduce the number of later-filed secondary patents aimed at extending market monopolies. The decision also serves the public policy objective of allowing others to build on the knowledge generated in the patent to develop follow-on compounds that may possess similar—or even enhanced—characteristics compared to the innovator compound.[203]

Indeed, this trial-and-error approach to innovating classes of drugs can allow latecomers to develop products that may be more safe or more effective than its precursors.[204] The decision may ultimately force companies to revisit their patent evergreening strategies. Patents may have to be filed earlier, with inventions more clearly disclosed and enabled, to avoid the invalidation of overly broad claims. In

197. Paul Michel & Matthew Dowd, Juno v. Kite*: A Rare Opportunity for the Supreme Court to Grant Rehearing*, IPWATCHDOG (Jan. 4, 2023, 4:15 PM), https://ipwatchdog.com/2023/01/04/juno-v-kite-rare-opportunity-supreme-court-grant-rehearing/ [perma.cc/Y9YH-665X].

198. Amgen v. Sanofi, 598 U.S. 594 (2023).

199. *Id.* at 616 ("Section 112 of the Patent Act reflects Congress's judgment that if an inventor claims a lot, but enables only a little, the public does not receive its benefit of the bargain. For more than 150 years, this Court has enforced the statutory enablement requirement according to its terms.").

200. Brief for Intellectual Property Professors as Amici Curiae in Support of Petitioners, at 11, Amgen v. Sanofi, 598 U.S. 594 (2023) (No. 21-757), https://www.supremecourt.gov/DocketPDF/21/21-757/251201/20230103084920246_Amicus%20Brief.pdf [perma.cc/Z5GT-MSXV].

201. *Id.* at 19.

202. *See generally* I-MAK, OVERPATENTED, OVERPRICED (2022).

203. The Supreme Court in *Amgen v. Sanofi* encapsulated the public policy rationale as follows: "So today, just as in 1790, the law secures for the public its benefit of the patent bargain by ensuring that, 'upon the expiration of [the patent], the knowledge of the invention [i]nures to the people, who are thus enabled without restriction to practice it.'" 598 U.S. 594, 604.

204. *See, e.g.*, Karin M. Torres-Obreque, Giovanna P. Menguetti, Jorge J. Muso-Cachumba, Valker A. Feitosa, Joao H.P.M. Santos, Sonia P.M. Ventura & Carlota O. Rangel-Yagui, *Building Better Biobetters: From Fundamentals to Industrial Application*, 27 DRUG DISCOVERY TODAY 65, 66–67 (2022).

that light, *Amgen v. Sanofi* could force inventors to disclose more at an earlier stage than they would otherwise be doing, which could limit product lifecycle management strategies like product hopping.

VII. PROCEDURAL ISSUES

One challenging aspect of patent law for would-be competitors is that the process is wrought with uncertainty: even patents with final office actions are never truly "final."[205] Until patents are published eighteen months after filing, there is no notice that applications have been submitted to USPTO. Nor is there any certainty that the patent will eventually be issued, as many published patent applications are abandoned prior to issuance. And even after a patent is rejected or issued, there are processes available to the patentee to revisit the patent document through continuations that may alter the scope of the previously issued patent.[206]

A. Patent Continuations under 35 U.S.C. § 120

In *Ending Abuse of Patent Continuations*, Mark A. Lemley and Kimberly A. Moore highlight three "pernicious consequences" of continuation practice: (1) delay and uncertainty among competitors, (2) overly broad patents due to the "wearing down" of patent examiners, and (3) submarine patents (where claims are modified in continuation to respond to competitor innovations).[207] Continuations take several forms, but generally occur when patent applicants are dissatisfied with either the proceedings or the outcome of patent prosecution at USPTO.[208] Both abandoned and issued patents can be continued, creating substantial uncertainty for would-be competitors.

1. Past: Submarine Patents

Historically, one problem was that publication and issuance could intentionally be delayed by the patentee for a long period of time. Submarine patents could "emerge" as issued after several years, causing disruptions to competitors that now have to grapple with potential infringement of the newly emerged patent. These patents were filed before patent terms changed in 1995, at which time patents lasted for seventeen years from the date of issuance. Thus, no matter how long the delay, a patentee would be guaranteed the full seventeen-year period once the patent was finally issued.

In 2021, the Federal Circuit determined the fate of 381 patent applications by notorious inventor Gilbert P. Hyatt.[209] All filed prior to the 1995 reforms, the court held that prosecution laches applied—Hyatt had forfeited his right to the patents because of his own unreasonable delay. The wearing down of patent examiners here

205. Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. REV. 63, 64 (2004).

206. *See* JOHN R. THOMAS, PATENT "EVERGREENING": ISSUES IN INNOVATION AND COMPETITION 5 (2009).

207. Lemley & Moore, *supra* note 205, at 65.

208. *Id.* at 64.

209. Hyatt v. Hirshfeld, 998 F.3d 1347 (Fed. Cir. 2021).

was significant: USPTO had to establish a special agency unit focused exclusively on Hyatt's applications.[210]

The practice was used in the pharmaceutical sector to protect Amgen's etanercept [Enbrel]: "[E]ven though the inventions involved were made in the early 1990s, the patents were not granted until 2011 and 2012 and last until 2028 and 2029."[211] Given that submarine patents had to be filed before 1995 and that recent ones were deemed to be unenforceable due to prosecution laches, they may not present much of an obstacle moving forward.

2. Present: Continuations as Quasi-Submarines

Though submarine patenting is a thing of the past, continuation patents have been used in similar ways. Once issued, patents are never truly "final"—patentees can continue negotiating with an examiner after a final office issue through a variety of mechanisms.[212] Tu and colleagues note, "[c]ontinuation patents can deter competition by increasing uncertainty for generic manufacturers, since they must avoid infringing (or must challenge) evolving patent claims on drugs."[213] By making minor clarifications or additions to existing patents—sometimes in response to actions by competitors—generic manufacturers have less clarity as to whether they are infringing patents covering the branded product prior to launching generic versions.[214] Tu and colleagues suggest that "continuation patents are becoming increasingly common in drug patent thickets, likely delaying or deterring generic competition, and thus potentially contributing to delays in patient access to generic medications and increases in health care spending."[215]

Tu and Charles Duan note that this process often entails broad initial written descriptions, with continuation patents that later narrow scope.[216] As an example, they point to a patent on the drug Vascepa that describes dosing amounts between 1 and 10,000 mg, 103 different concentrations, and treatment periods of between 1 and 200 weeks.[217] They reason that "the written description doctrine is failing to sufficiently police these 'laundry list' patents of questionable innovative value."[218]

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210. Perry Cooper & Susan Decker, *Hundreds of 'Submarine Patents' Likely in Peril After Ruling*, BLOOMBERG LAW (Jun. 2, 2021, 1:47 PM), https://www.bloomberglaw.com/bloomberglawnews/ip-law/XBSNG1R8000000.

211. Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions*, N.Y. TIMES (July 15, 2016), https://www.nytimes.com/2016/07/16/business/makers-of-humira-and-enbrel-using-new-drug-patents-to-delay-generic-versions.html [web.archive.org/web/20160716061515/https://www.nytimes.com/2016/07/16/business/makers-of-humira-and-enbrel-using-new-drug-patents-to-delay-generic-versions.html].

212. Sean Tu, *Understanding the Backlog Problems Associated with Requests for Continued Examination Practice*, 13 DUKE L. & TECH. REV. 216, 220 (2015) ("If the action is a final Office action, then the applicant can: (1) file an after final response (which may or may not be entered into the record by the examiner), (2) abandon the application, (3) appeal the rejection to the Patent Trial and Appellate Board (PTAB), or (4) try to continue the negotiation with the examiner.").

213. S. Sean Tu, Aaron S. Kesselheim, Kathrine Wetherbee & William B. Feldman, *Changes in the Number of Continuation Patents on Drugs Approved by the FDA*, 330 JAMA 469 (2023).

214. *See, e.g.*, Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1479 (Fed. Cir. 1998) (inventor admitted at trial that patent claims were amended in response to actions by competitors).

215. Tu et al., *supra* note 213, at 470.

216. S. Sean Tu & Charles Duan, *Pharmaceutical Patent Two-Step: The Adverse Advent of* Amarin v. Hikma Type *Litigation*, 12 N.Y.U J. INTELL. PROP. & ENT. L. 1, 26 (2022).

217. *Id.* at 34.

218. *Id.* at 36.

Given the widespread use of continuations to delay or deter competition, Lemley and Moore argue that USPTO could abolish continuations for pharmaceutical patents altogether.[219] Would-be competitors deserve to know with some certainty both the number and scope of patents covering a given pharmaceutical, such that it can, with reasonable certainty, produce a non-infringing copy of that product when market exclusivity ends.

B. Patent Term Extensions Under 35 U.S.C. § 156

Drug and biologic patent terms can be extended by a period of up to five years to account for time spent in clinical testing and regulatory review.[220] Generally, the patent term restoration applies to the active ingredient (primary patent). However, two modern Federal Circuit decisions have upheld the awarding of patent term restoration to the active ingredients of product hops, despite the fact those patents would be considered secondary in the context of the precursor drug.[221] For product hops in which a secondary patent later becomes a follow-on drug's primary patent (such as with enantiomers), USPTO should not grant a second patent term restoration period on public policy grounds.

VIII. LEGAL/REGULATORY APPROACHES

Perhaps the most straightforward solution to the overpatenting of pharmaceuticals is to curtail regulatory incentives to marketing those products. In Europe, for instance, manufacturers have little incentive to market product hops because no additional periods of regulatory exclusivity can be awarded for products with the same chemical entity.[222] In fact, a manufacturer must demonstrate that its new product is "exceptional" to receive a single additional year of exclusivity.[223] But the U.S. pharmaceutical industry would be strongly opposed to such a regulatory reform and would likely assert that Congress is attempting to "stifle innovation."[224] Yet the unspoken part of this narrative is that Congress would only be stifling the

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219. Lemley & Moore, *supra* note 205, at 93–94.

220. Reed F. Beall, Jonathan J. Darrow & Aaron S. Kesselheim, *Patent Term Restoration for Top-Selling Drugs in the United States*, 24 DRUG DISCOVERY TODAY 20, 20 (2019) ("Examining 170 top-selling drugs with a first generic equivalent approved between 2000 and 2012, we found that 49% (83 drugs) received a PTR extension (median extension: 2.75 years) yielding a median total exclusivity period of 13.75 years, compared with 10.0 years for the 87 nonextended drugs."); *see also* Aaron S. Kesselheim, Michael S. Sinha, Jerry Avorn & Ameet Sarpatwari, *Pharmaceutical Policy in the United States in 2019: An Overview of the Landscape and Avenues for Improvement*, 30 STAN. L. & POL'Y REV. 421, 446–47 (2019).

221. Two Federal Circuit cases affirmed the awarding of patent term extensions to a reformulated drug (*Photocure ASA v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2009)) and an enantiomer drug (*Ortho-McNeil Pharmaceutical, Inc. v. Lupin Pharmaceuticals, Inc.*, 603 F.3d 1377 (Fed. Cir. 2010)); *see also* MARTIN A. VOET, THE GENERIC CHALLENGE: UNDERSTANDING PATENTS, FDA AND PHARMACEUTICAL LIFE-CYCLE MANAGEMENT 20 (6th Ed. 2020).

222. Michael S. Sinha, Sven J.R. Bostyn & Timo Minssen, *Addressing Regulatory Exclusivity Issues During the COVID-19 Pandemic*, *in* COVID-19 AND THE LAW: DISRUPTION, IMPACT, AND LEGACY 239 (I. Glenn Cohen, Abbe D. Gluck, Katherine Kraschel & Carmel Shachar eds., 2023).

223. *Id.*

224. *See* Michael A. Carrier & Genevieve Tung, *The Industry That Cries Wolf: Pharma and Innovation*, STAT NEWS FIRST OPINION (Sept. 26, 2019), https://www.statnews.com/2019/09/26/innovation-boy-cried-wolf-pharma-industry/ [perma.cc/3448-FJRY].

costly incremental innovation that costs payers billions while offering only marginal gains over existing therapy.[225]

Another reason product hops can have commercial success despite their limited clinical utility over existing products is that they are not automatically substitutable at the pharmacy level.[226] In their 2018 Health Affairs blog post, Arti K. Rai and Barak D. Richman recommend the implementation of a "suitability petition."[227] Upon submission of such a petition to the FDA, the agency would approve generic equivalents of pioneer compounds as alternatives to branded product hops.[228] Allowing such flexibility in generic substitution may discourage brand manufacturers from producing products with small tweaks in order to preserve market share from generics.[229] For instance, state automatic substitution laws at the pharmacy level could be expanded to allow more costly extended-release formulations to be substituted for less costly generic instant-release versions, generating cost savings for payers and patients.[230]

Taken further, the standards for interchangeability could match that of bioequivalence. If your NDA (New Drug Application) for an extended-release formulation, for instance, relies on the prior NDA for the instant-release formulation, pharmacies should still be able to automatically substitute generics when scripts for the extended-release formulation are written. This may mean changes to dosing regimens, but those can be easily explained to patients and justified by cost savings. Moreover, if either the physician or the patient insists on use of the new formulation, a physician can always write "brand medically necessary" or "do not substitute" on the prescription. Even with aggressive pharmaceutical detailing, only in limited circumstances is a physician likely to deem the brand "medically necessary."

Michael A. Carrier and Steve D. Shadowen, in *Product Hopping: A New Framework*, argue for the broad use of a "no-economic-sense" test by "courts, government enforcers, plaintiffs, and manufacturers."[231] The central question here is "whether the hop would make business sense for the brand manufacturer if it did not have the effect of impairing generic competition."[232] In 2021, a bill incorporating these principles—the Affordable Prescriptions for Patients Act—was

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225. Rachel Goode & Bernard Chao, *Biological Patent Thickets and Delayed Access to Biosimilars, An American Problem*, J. L. & BIOSCIS., July–Dec. 2022, at 1.

226. In the FDA's *Orange Book of Approved Drug Products with Therapeutic Equivalence Evaluations*, only drugs with an AB designation are interchangeable. Product hops evade this designation: generics only have an AB designation with respect to the original branded product, not the reformulated "product hop."

227. Arti K. Rai & Barak D. Richman, *A Preferable Path for Thwarting Pharmaceutical Product Hopping*, HEALTH AFFS. BLOG (May 22, 2018), https://www.healthaffairs.org/content/forefront/preferable-path-thwarting-pharmaceutical-product-hopping [perma.cc/GK6Z-KSEV].

228. *Id.*

229. *Id.*

230. *Id.* Rai and Richman use the example of Namenda XR and Namenda IR. The manufacturer, Actavis, planned to switch patients to extended-release version Namenda XR and remove Namenda IR from the market prior to market exclusivity expiration. This would have created a population of patients on Namenda XR, insulated from competition by generics of Namenda IR. New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638 (2d Cir. 2015).

231. *See* Carrier & Shadowen, *supra* note 1, at 168.

232. *Id.* at 170 ("If a brand acquires or maintains monopoly power by engaging in product hopping that fails the no-economic-sense test, courts should find it liable for illegal monopolization since the behavior makes no sense other than by stifling generic competition.").

introduced in the U.S. Senate.[233] In addition to identifying the harm associated with hard switches, the legislation also addresses "soft switches in which the [manufacturer] (1) unfairly disadvantages the original and impedes competition and (2) sells a follow-on drug."[234] The bill explicitly authorizes the FTC to investigate and challenge problematic product hops. In July of 2024, the United States Senate unanimously passed a scaled-back version of the bill that stripped its product hopping provisions.[235]

Other reforms to the Hatch-Waxman Act of 1984 and the Biologics Price Competition and Innovation Act (BPCIA) of 2010 could also help disincentivize the aggregation of patents to protect lucrative brand-name products. Both laws incentivize settlement of patent infringement litigation, which generally leaves patents in force while allowing the brand manufacturer to control the timing of generic entry by competitors. Reforms to the Hatch-Waxman Act that eliminate the thirty-month stay for patent litigation[236] or award longer duopoly periods than 180 days for successful patent invalidation might incentivize would-be generic competitors to see patent litigation to its conclusion, resulting in the invalidation of more patents. Moreover, the 180-day period could be opened in the context of settlements, not pushed off to be put in force when the first entrant agrees to market its product.[237] Similarly, amending BPCIA to either eliminate the patent dance or reform it to allow more patents to be challenged in a single case while disincentivizing settlement might similarly drive patent infringement litigation toward court opinions rather than settlements.

Finally, *inter partes* review (IPR) proceedings initiated by challengers should proceed to determination regardless of whether parties settle their dispute.[238] Sean Tu and Mark Lemley note that though IPR may be inefficient in the setting of patent thickets and cannot lift the thirty-month stay, the program was "designed to lower the cost of invalidating patents . . . [and] might be a solution to the problem of bad follow-on pharmaceutical patents."[239]

As noted above, there are real opportunities for agency collaboration to reduce the incidence and mitigate the impact of product hopping through regulatory

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233. Carrier, *supra* note 63, at 2.

234. *Id.* Carrier notes that "Legislation giving the FTC the power to challenge anticompetitive product hopping is the best option to ensure that this conduct does not evade scrutiny." *Id.* at 3.

235. Tristan Manalac, *Senate Unanimously Passes Bill to Reduce Big Pharma Patent Thickets, Increase Competition*, BIOSPACE (July 12, 2024), https://www.biospace.com/policy/senate-unanimously-passes-bill-to-reduce-big-pharma-patent-thickets-increase-competition [perma.cc/FM4P-MYHR].

236. *But see* Sunand Kannappan, Jonathan J. Darrow, Aaron S. Kesselheim & Reed F. Beall, *The Timing of 30-Month Stay Expirations and Generic Entry: A Cohort Study of First Generics, 2013–2020*, 14 CLINICAL & TRANSLATIONAL SCI. 1917, 1917 (2021) ("30-month stays are unlikely to delay the timing of generic entry.").

237. Michael A. Carrier, *Solving the Drug Settlement Problem: The Legislative Approach*, 41 RUTGERS L.J. 81, 97–98 ("By paying this first-filer to delay entering the market, the brand firm is able to delay entry by all generic firms. For this generic's 180-day exclusivity period begins to run only when it actually enters the market. If the first filer settles its patent challenge with the brand firm by agreeing not to enter the market, the incentive to challenge invalid patents at the heart of Hatch Waxman is subverted.").

238. Victor L. Van de Wiele, Aaron S. Kesselheim & S. Sean Tu, *Biologic Patent Challenges Under the America Invents Act*, 42 NATURE BIOTECHNOLOGY 374, 374 (2024).

239. S. Sean Tu & Mark A. Lemley, *What Litigators Can Teach the Patent Office About Pharmaceutical Patents*, 99 WASH. U. L. REV. 1673, 1682–83 (2022).

reform.[240] Recent dialogue between the FDA and USPTO is a start, and the recommendations herein offer a good starting point for collaborative efforts. Other stakeholders like the FTC should be a part of these discussions as well, helping USPTO and FDA flag patent applications that may lead to anticompetitive product hops.

These regulatory and legal reforms would complement the patent-centered approach I have outlined by decreasing the incentive to patent—and subsequently pursue FDA approval for—incremental variations of lucrative blockbuster drugs.

CONCLUSION

In the pharmaceutical sector, incremental innovation has arguably surpassed transformative innovation. And even when research and development has been transformative, the technologies have become so thoroughly protected by patents and trade secrets as to create a tragedy of the anticommons—in which no manufacturer has the freedom to operate or to produce the product.[241]

As drug pricing continues to escalate to dramatic levels while new products become less innovative and less well characterized prior to marketing—an ignoble "race to the bottom"—payers and patients must demand both higher-quality medications as well as timely access to generics and biosimilars, such that prices fall after a clearly-defined period of market monopoly. By elevating standards of patentability in ways that limit the aggregation of weak patents for lucrative pharmaceutical products, we can limit product hops of lucrative brand name products while fostering a competitive marketplace for generics and biosimilars in the future.

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240. Sinha, *supra* note 7, at 445–46 ("Screening product hops for anticompetitive potential at the point of FDA review would be more efficient than enforcement by FTC months to years after the harm to patients and payers has occurred. Importantly, the FDA's own NDA classification system makes this relatively easy for the agency to administer.").

241. For instance, the mRNA vaccines against COVID-19 are protected by thickets of patents, which has culminated in litigation between the two major manufacturers, Moderna and Pfizer. *See* ModernaTX, Inc. v. Pfizer, Inc., No. 22-11378, 2023 WL 4907602 (D. Mass. 2022).