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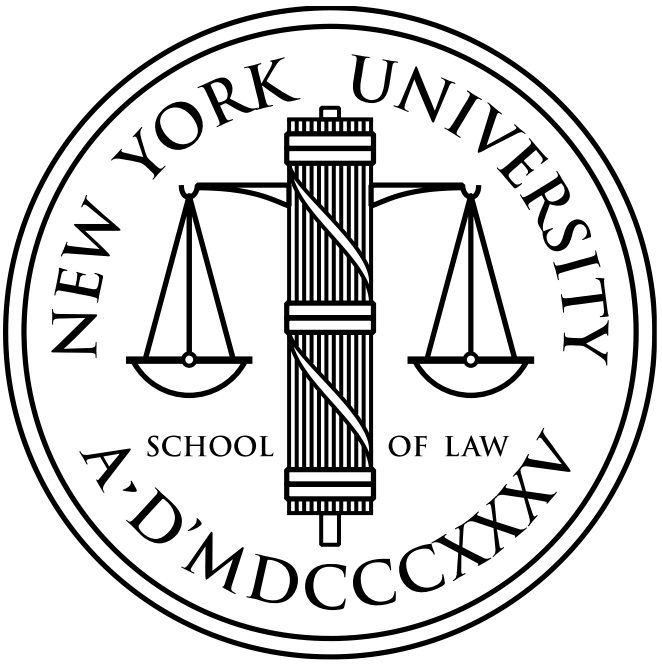

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PHARMACEUTICAL PATENT TWO-STEP: THE ADVERSE ADVENT OF *AMARIN V. HIKMA* TYPE LITIGATION*

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Pharmaceutical companies have long sought to maintain exclusivity over market drugs in a myriad of ways including creating patent thickets and evergreening. This article describes a two-step strategy by which pharmaceutical companies attempt to keep market exclusivity and delay generic entry. This new strategy can work in tandem with ANDA litigation and FDA labeling requirements to reclaim exclusive rights that should have expired or been unavailable under patent law.

The "first wave" of litigation involves a typical ANDA litigation, where brand manufacturers sue for patent infringement to prevent generics from entering the market. The "second wave" of litigation involves suing the generic for induced infringement based on the "skinny label" on the generic drug. Notably, this second wave of litigation can act regardless of if the brand firm wins or loses the first wave of litigation.

In this article we use Amarin v. Hikma *as a case study of this strategy. We show that after the generic firm Hikma won the ANDA litigation invalidating a set of patents, they were subjected to a second wave of litigation based on a new set of patents. In this article we examine this new strategy and take a deep dive into the patent portfolios to*

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determine how Amarin was able to create a large method of use-based patent thicket to set up this second wave of litigation.

Although Hikma was able to win both the first and second waves of litigation, these court cases raise transaction costs and may deter or delay generic entry. These delays can amount to billions of added dollars to drug costs. This second wave strategy is especially important after the landmark GlaxoSmithKline v. Teva *case, which could breathe new life into this type of litigation strategy.*

INTRODUCTION

Only in the world of pharmaceutical patents can one have two bites at the litigation apple. Amarin is the patent holder on and manufacturer of the

cardiovascular drug Vascepa (icosapent ethyl).[1] When generic firm Hikma sought to enter the market, Amarin brought a "first wave"[2] patent infringement suit to block the competing product, but lost.[3] In response to this loss, Amarin brought a "second wave" patent infringement suit based on an induced infringement theory.[4] Amarin lost again.[5] Without a meritorious patent case from Amarin, Hikma's cost-saving generic product ought to have been approved and available arguably as early as 2016.[6] And yet with Vascepa earning Amarin roughly $580 million per year, the undue profits from years of litigation made those failed lawsuits worthwhile.[7]

The litigation between Amarin and Hikma exemplifies how brand-name pharmaceutical manufacturers try to extend the life of their exclusive rights to charge supracompetitive prices. The amount of money associated with just one erroneously protected drug can amount to billions of dollars.[8] While previous studies have discussed both "evergreening" and creation of "patent thickets" as strategies for brand firms to delay or prevent generic drug market entry,[9] the patent enforcement strategies based on these patent portfolios has received less attention.

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[1] *Amarin Reports Fourth Quarter and Full Year 2021 Financial Results and Provides Business Update*, Amarin (Mar. 1, 2022), at *4, https://investor.amarincorp.com/news-releases/news-release-details/amarin-reports-fourth-quarter-and-full-year-2021-financial.

[2] The "first wave" and "second wave" terminology is used to avoid confusion with "primary" and "secondary" patents which have a different meaning. First wave patents are those patents that are associated with the ANDA litigation or are the patents that cover the drug product's active ingredient. First wave patents are usually associated with primary patents. Second wave patents for purposes of this article are "methods of use" patents associated with specific Orange Book use codes.

[3] *See* Ian Lopez, *Teva Drug-Label Case Spurs Fresh Litigation as Judges Weigh Redo*, Bloomberg L. News (Mar. 8, 2021, 5:31 AM), https://www.bloomberglaw.com/bloomberglawnews/health-law-and-business/XDL3PJD0000000?bna_news_filter=health-law-and-business#jcite; *see also* Amarin Pharma v. Hikma Pharms. USA Inc. (*Amarin I*), 449 F. Supp. 3d 967, 1015 (D. Nev. 2020) (finding all Amarin infringement claims as invalid).

[4] Amarin Pharma v. Hikma Pharms. USA Inc. (*Amarin II*), 578 F. Supp. 3d 642, 644 (D. Del. 2022) ("Plaintiffs sued Defendants for induced infringement of three patents that describe methods of using icosapent ethyl for the reduction of cardiovascular risk.).

[5] *Amarin II*, 578 F. Supp. 3d at 643 (granting Hikma's motion to dismiss).

[6] *Amarin I*, 449 F. Supp. 3d at 974–75 (noting 2016 as the filing date of Amarin's application for approval of the generic product).

[7] *Amarin Reports Fourth Quarter and Full Year 2021 Financial Results*, *supra* note 1, at *1.

[8] David Miller, Benedic Ippolito, Inmaculada Hernandez & Benjamin Davies, *The Costs of Delayed Generic Drug Entry: Evidence from a Controversial Prostate Cancer Drug Patent*, 37 J. Gen. Internal Med. 668, (2021) (showing that an inappropriately awarded secondary patent cost consumers $2 billion).

[9] Robin Feldman, *May Your Drug Price be Evergreen*, 5 J.L. Biosciences 590, (2018); Bronwyn H. Hall, Christian Helmers & Georg von Graevenitz, *Technology Entry in the Presence of Patent Thickets* (Nat'l

This article focuses on attempts to extend exclusivity or delay generic market entry based on a two-step litigation strategy. First, brand manufacturers will sue generic manufacturers for violating a first wave of patents in the context of Abbreviated New Drug Application (ANDA) litigation.[10] If the brand manufacturers lose the ANDA litigation, then they will try for a second bite at the apple by suing the generic manufacturer on an "induced infringement" theory based on a second wave of patents directed to the drug's "methods of use."[11] A recent Federal Circuit case, *GlaxoSmithKline v. Teva* (*GSK II*), has opened the door for these types of arguments, challenging Supreme Court precedent to the contrary and upending a thirty-year "skinny label" system that has been proven to bring low-cost generics to market.[12] Now there is a wave of lawsuits filed challenging the use of skinny labels and more of these suits will likely be on the way.[13]

We use *Amarin Pharma v. Hikma Pharms.* as a case study to show how brand manufacturers are abusing Food & Drug Administration (FDA) labeling requirements to delay or deter Amarin Igenerics from entering the market.[14] In this paper we examine the patents asserted in both the ANDA litigation and the labeling litigation.[15] We examine the patent prosecution histories as well as the patent filing strategies used to create large portfolios of similar patents created only to delay entry.[16] The patent disclosures for Vascepa's use codes in these secondary patents were minimal, and the validity of the patents under the written description and enablement requirements of patentability are questionable at best.[17] Furthermore, these patents come from large and related patent families only minimally advance innovation and do not justify the exclusive rights associated with patents or the use codes listed in the Orange Book.

Bureau Econ. Rsch., Working Paper No. 21455, 2015) (showing that patent thickets raise entry costs and lead to less entry into technologies regardless of a firm's size).

[10] *See* 35 U.S.C. § 271(e)(2)(A) (2018).

[11] *See infra* Parts I.D–E.

[12] *See* GlaxoSmithKline LLC v. Teva Pharms. USA, Inc. (*GSK II*), 7 F.4th 1320, 1326 (Fed. Cir. 2021) (holding Teva infringed on GSK patents under an inducement theory); *see also* Lopez, *supra* note 3 (highlighting that at least five lawsuits were brought following the Teva patent decision); *but see* Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 566 U.S. 399 (2012).

[13] Lopez, *supra* note 3.

[14] *Amarin I*, 449 F. Supp. 3d 967, 1015 (D. Nev. 2020).

[15] *See infra* Part III.A.

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

[17] *See infra* Part III.C-D.

Amarin's tactics suggest a concerted effort to delay generic entry by filing a multi-layered patent thicket based not only the first-wave patent claims, but also the FDA use codes associated with a set of second-wave patents. The U.S. Patent and Trademark Office (PTO) and the FDA need to coordinate examination of these important patents to prevent creation of these large patent portfolios that do not benefit the public with new innovations, but rather serve primarily to delay or deter generics from market entry.[18]

I
The Hatch-Waxman Act: ANDA Litigation & Skinny Label Litigation

ANDA litigation and skinny labeling serve two separate and distinct purposes. ANDA Paragraph IV litigation provides a path for generics to get to market faster by giving generics an incentive to challenge weak patents that may prevent market entry. To forestall generic entry, brand firms have increased the number of patents that cover each drug product, creating "patent thickets." Patent thickets are overlapping sets of patent rights that help prevent market entry by creating uncertainty and added risk for potential market entrants. Many of these patent thickets are stocked with weak secondary patents,[19] many of which are directed towards multiple "methods of use" claims.[20]

Method of use patents present a particular problem for generic manufacturers because they commonly have expiration dates that far exceed the original composition of matter claims (primary patents).[21] For example, in 2012 the drug Vascepa had only one indication (treatment for disease) authorizing use only

[18] S. Sean Tu, *FDA Reexamination: Increased Communication Between the FDA and USPTO to Improve Patent Quality*, Hous. L. Rev. (forthcoming 2023).

[19] Secondary patents are follow-on patents that are usually weaker and invalidated at a higher rate. *See* S. Sean Tu & Mark A. Lemley, *What Litigators Can Teach the Patent Office About Pharmaceutical Patents*, 99 Wash. U.L. Rev. 1673, 1712 (2022). Secondary patents usually include formulation, methods of use and enantiomer and polymorph claims. *See id.* at 1691. In contrast, primary patents are directed towards the drug's active pharmaceutical ingredient. *See id.* (stating that "primary" patents are "directed to new chemical entities").

[20] Tu & Lemley, *supra* note 19, at 1691 (fig.3, showing that 94% of invalidated Orange Book patents were secondary patents).

[21] Primary patents are directed towards the drug's active pharmaceutical ingredient. Primary patents are usually the strongest patents that usually do not get invalidated during litigation. Generic manufacturers usually wait until the expiration of these patents before entering the market. *See* Reed F. Beall, Jonathan J. Darrow & Aaron S. Kesselheim, *Approximating Future Generic Entry for New Drugs*, 47 J.L., Med. & Ethics 177, 177 (2019).

for reducing triglyceride levels in patients with severe hypertriglyceridemia.[22] Currently, however, Vascepa has 40 indications, with most indications directed to patients with cardiovascular disease.[23] Although the first Orange Book patents listed in 2013 expired in January 2020,[24] current patents based on methods of use attempt to extend the life of the drug to June 2033.[25]

To allow generic companies to overcome these method of use claims, Congress created a process called "skinny labeling."[26] This process allows generic companies to "carve out" those drug indications that are no longer under patent protection, while avoiding infringement of those indications that are still under patent protection.[27] Thus, skinny labels allow generic companies to include only those indications that are unpatented on the label while excluding the patented indications.

In the sections below we briefly outline the new drug approval process, the use codes associated with the new drug applications, and how labeling interacts with the FDA approval process. We then describe the current state of skinny labeling jurisprudence.

A. New Drug Applications (NDAs)

The Hatch-Waxman Act attempts to balance innovation and access to pharmaceuticals. It gives special rights to pharmaceutical patent owners, including longer patent terms[28] and the power to prevent a generic drug from receiving FDA

[22] Letter from Eric Colman, U.S. Food & Drug Admin., to Peggy Berry, Amarin Pharma Inc., NDA Approval: NDA 202057 (July 26, 2012), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202057Orig1s000ltr.pdf.

[23] *See* Appendix 2 for a list of all the use codes associated with Vascepa.

[24] U.S. Patent No. 8,188,146 listed under NDA 202057. *See* U.S. Food & Drug Admin., Approved Drug Products with Therapeutic Equivalence Evaluations 1167 (33d ed. 2013) [hereinafter The Orange Book, 2013].

[25] Numerous patents listed under NDA 202057 have an expiration date of June 28, 2033. *See* U.S. Food & Drug Admin., Approved Drug Products with Therapeutic Equivalence Evaluations 1396-98 (42d ed. 2022) [hereinafter The Orange Book, 2022]; *see also* Appendix 1 (Orange Book patents associated with Vascepa).

[26] *See* Bryan Walsh, *Skinny Labeling: A Pathway for Timely Generic Drug Competition*, Commonwealth Fund (Oct. 19, 2021), https://www.commonwealthfund.org/blog/2021/skinny-labeling-pathway-timely-generic-drug-competition.

[27] *See id.*

[28] *See* 35 U.S.C. § 156 (2018).

approval to enter the market for up to thirty months until any patent litigation is resolved—in effect, an automatic preliminary injunction.[29]

Patents subject to these rules are listed with the FDA in an FDA compendium commonly known as the Orange Book. The rules require that applicants for new drug applications (NDAs)

> shall file with the application the patent number and the expiration date of any patent which claims the drug . . . or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.[30]

In other words, this FDA process requires that all patents associated with new drugs are listed in the Orange Book.[31] Specifically, the FDA requires patents that "consist of drug substance (active ingredient) patents, drug product (formulation and composition patents), and method-of-use patents" to be listed in the Orange Book.[32] Applicants may not list process patents, patents claiming packaging, patents claiming metabolites, or patents claiming intermediates.[33] In addition to the patent number and expiration dates,[34] the FDA requires a description of any method-of-use patents, known as a use code.[35]

Importantly, the FDA does not substantively review the accuracy of the patent information before publishing.[36] This is because the FDA interprets its role in listing patent information as "purely ministerial" and explained that it "lacks both

[29] *See* 21 U.S.C. § 355(j)(5)(B)(iii) (2018). By contrast, actual preliminary injunctions in patent cases are quite rare. *See* High Tech Med. Instrumentation, Inc. v. New Image Indus., Inc., 49 F.3d 1551, 1554 (Fed. Cir. 1995) ("[A] preliminary injunction is 'not to be routinely granted.'" (quoting Intel Corp. v. ULSI Sys. Tech., Inc., 995 F.2d 1566, 1568 (Fed. Cir. 1993))).

[30] 21 U.S.C. § 355(b)(1) (2018)

[31] *Id.* Most new drugs are protected by one or more patents.

[32] 21 C.F.R. § 314.53(b)(1) (2022).

[33] *Id.*

[34] *Id.*

[35] Matthew M. D'Amore, Steve Keane & David C. Doyle, *FDA (Finally!) Issues New Regulations to Clarify Pharmaceutical Patent Litigation: How to Use Patent "Use Codes,"* 29 Intell. Prop. & Tech. L.J. 10, 10 (2017).

[36] D'Amore, Keane & Doyle, *supra* note 35, at 10.

the resources and the expertise to police the correctness…of every patent listing submitted by an NDA holder."[37]

The mere listing of a patent in the Orange Book can delay competition for months, or even years, and drive-up expenses for competitors.[38] Accordingly, drug companies have liberally interpreted those patents that can or should be listed in the Orange Book. For example, some Orange Book patents have included mechanical devices,[39] or even design patents.[40]

B. Abbreviated New Drug Applications (ANDAs)

Under the Hatch-Waxman Act, after the FDA has approved a brand manufacturer's drug, another company may seek permission to market a generic version by filing an ANDA.[41] An ANDA relies on the data the brand firm submitted to the FDA to receive quicker approval for a generic version of the same drug.[42]

The FDA, however, cannot authorize a generic drug that would infringe a brand manufacturer's patent. As part of the ANDA process, the generic manufacturer must review the Orange Book, and then make a certification for non-infringement (for each patent listed in the Orange book).[43] A certification of non-infringement may be made in one of four ways: (1) the NDA holder has not submitted patent information to the FDA for listing in the Orange Book; (2) the patent has expired; (3) the date the patent will expire; or (4) "[the] patent is invalid

[37] aaiPharma Inc. v. Thompson, 296 F.3d 227, 237 (4th Cir. 2002) (noting that the FDA does not substantively review the correctness of the patent information before publication); *see also* Teva Pharms. USA, Inc. v. Leavitt, 548 F.3d 103, 106 (D.C. Cir. 2008); Am. Bioscience, Inc. v. Thompson, 269 F.3d 1077, 1084 (D.C. Cir. 2001); 21 C.F.R. § 314.53(e) (2022); 68 Fed. Reg. 36,683 (June 18, 2003).

[38] Jake Holdreith & Emily Tremblay, *Listing Device Patents in the Orange Book: Can You Do That?*, Robins Kaplan (May 8, 2018), https://www.robinskaplan.com/resources/blog-posts/2018/05/listing-device-patents-in-the-orange-book-can-you-do-that.

[39] *See, e.g.*, U.S. Patent Nos. 7,449,012; 7,794,432; 8,048,035; 8,870,827; 9,586,010; 9,526,844 (epipen automatic injector). Other types of drug device patents listed on the Orange Book include pre-filled syringes and respiratory inhalers.

[40] *See, e.g.*, U.S. Patent No. D468424 (Swabstick).

[41] *See* 21 U.S.C. § 355(j)(2)(A)(ii), (iv).

[42] *Id.*

[43] *See* 21 U.S.C. § 355(b)(2)(A) (requiring certification for applicants submitting a drug for which they did not conduct initial drug trials); see also 21 U.S.C. § 355(j)(2(A)(vii) (ANDA process).

or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted."[44]

Thus, ANDAs encourage generics to challenge the branded patents before they expire. When generic firms believe that the relevant patents are either invalid or do not cover the generic product, they may file a "Paragraph IV" certification to challenge these patents as either invalid or non-infringed.[45] If the patent(s) are found to be invalid, then the generic company can enter the market before the patent expires. Filing a Paragraph IV certification is deemed by law to be an act of infringement to which the brand-name firm can respond by filing a patent infringement suit.[46]

To encourage generic firms to engage in Paragraph IV certifications, the first generic applicant who files a Paragraph IV certification is given a 180-day exclusive right to market its product in competition with the brand-name firm before other generic firms may enter the market.[47]

These challenges are expensive, complex, and subject to gamesmanship.[48] Patentees try to extend patent lifecycles by creating large patent thickets and "evergreening" their patents, adding new patents on minor variants as the basic patents expire.[49] The structure of the regulatory regime means that all patents, no matter how weak, pose a significant obstacle to generic market entry.

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[44] 21 U.S.C. §§ 355(b)(2)(A), (j)(2)(A)(vii). This last is commonly referred to as a "Paragraph IV" certification.

[45] C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents?*, 8 J. Empirical Legal Stud. 613, 624 (2011) (fig. 4 showing that 299 out of 692 drugs were subjected to Paragraph IV challenges).

[46] *See* 21 U.S.C. § 355(c)(3)(C) (for 505(b)(2) NDAs); (j)(5)(B)(iii) (for ANDAs).

[47] 21 U.S.C. § 355(j)(5)(B)(iv).

[48] AIPLA 2021 Report of the Economic Survey at 67 and I-158 to I-161 (showing (1) an average cost of $2.608 million when $1-10 million is at risk, (2) an average cost of $6.219 million when more than $25 million is at risk, and (3) an average cost of $774 thousand for filing or defending a PGR/IPR in Life Sciences). *See* Jeremy Bulow, *The Gaming of Pharmaceutical Patents*, Innovation Pol'y & Econ. 145, 145–87 (A.B. Jaffe, J. Lerner & S. Stern eds., 2004); C. Scott Hemphill, *Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem*, 81 N.Y.U. L. Rev. 1553 (2006).

[49] Hemphill & Sampat, *supra* note 45, at 615 (2011) (noting that "[b]rand-name firms have sought increasing recourse to ancillary patents on chemical variants, alternative formulations, methods of use, and relatively minor aspects of the drug"); Gideon Parchomovsky & R. Polk Wagner, *Patent Portfolios*, 154 U. Pa. L. Rev. 1, 5–6, 27 (2005); Hall, Helmers & von Graevenitz, *supra* note 9 (showing that patent thickets raise entry costs and lead to less entry into technologies regardless of a firm's size).

Why do brand firms stockpile weak patents that inevitably end up invalidated? One explanation is that even short delays in market entry can garner millions of dollars in added revenues. Since many of these blockbuster drugs make billions of dollars each year, brand firms are incentivized to spend millions of dollars on frivolous lawsuits even if the result is only a short delay in market entry.[50] For example, Abbvie's adalimumab (Humira), which is the world's top revenue-generating brand-name drug, generated $17.3 billion in 2021 alone.[51] Based on that 2021 revenue value, a one-day delay would generate $47.4 million. So long as Abbvie's litigation costs are under $47 million, one day's revenue would pay for the average litigation seven times over.[52]

C. Orange Book: FDA Use Codes

ANDA applicants can attack unexpired methods of use patents using a Paragraph IV certification.[53] Additionally, if the brand firm has unexpired method of use patents, the ANDA applicant can also file a "section viii" statement asserting that it will market the drug for only those methods of use not covered by the brand's patent(s).[54] The ANDA applicant must also propose a label that "carves out" the still-patented method(s) of use.[55] The FDA will not approve an ANDA if the proposed label overlaps at all with the brand's use code.[56]

FDA use codes are how the brand firm tells the FDA how their Orange or Purple Book listed method patents relate to their approved drug indications.[57]

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[50] In reality, brand firms do not even need to bring frivolous lawsuits because under the Hatch-Waxman Act the generic firms are the ones who are required to bring suits to invalidate these weak patents. This regulatory structure rewards brand firms to create large patent thickets composed of relatively weak patents.

[51] Press Release, AbbVie, AbbVie Reports Full-Year and Fourth-Quarter 2021 Financial Results (Feb. 2, 2022) (on file with author), https://news.abbvie.com/news/press-releases/abbvie-reports-full-year-and-fourth-quarter-2021-financial-results.htm.

[52] The AIPLA 2021 Report of the Economic Survey shows that companies spend an average of $6.219 million on litigation costs when more than $25 million is at risk. *See* AIPLA 2021 Report at 67 and I-161.

[53] 21 U.S.C. § 355(j)(2(A)(vii).

[54] 21 U.S.C. § 355(j)(2(A)(viii).

[55] 21 C.F.R. § 314.94(a)(8)(iv) (2022).

[56] *Caraco Pharm*, 566 U.S. at 405 ("[T]he FDA cannot authorize a generic drug that would infringe a patent . . .").

[57] "The Purple Book is a database that contains information about all FDA-licensed biological products regulated by the Center for Drug Evaluation and Research (CDER), including licensed biosimilar and interchangeable products, and their reference products." *Purple Book Database of Licensed Biological Products*, U.S. Food & Drug Admin., https://purplebooksearch.fda.gov/about (last visited, Nov. 1, 2022).

Method patents typically claim how a drug substance or product is used to treat an indication (disease). For example, US Patent No. 6,958,335 is directed to "[a] method of treating gastrointestinal stromal tumors which comprises administering to a human in need of such treatment a dose, effective against gastrointestinal stromal tumors, of <imatinib>."[58]

Each method claim can also have an associated use code. For example, Novartis' imatinib (Gleevec) was initially approved in 2001 for treatment of patients with chronic myeloid leukemia (CML).[59] The first wave patent (US Pat. No. 5,521,184, herein the '184 patent) was directed towards the composition of matter and expired in 2015.[60] By 2018, Novartis listed three different uses for imatinib. US Pat. No. 6,894,051 ('051 patent) had a use code of "U-649"[61] and US Pat. No. 6,958,335 ('335 patent) had use codes "U-1883"[62] and "U-791"[63] and expired on May 23, 2019, and December 19, 2021, respectively.[64] The '051 and '335 patents both had use codes directed towards the use of imatinib to treat Gastrointestinal Stromal Tumors (GIST).[65] By waiting for the '184 patent to expire and then using a skinny label to exclude the patented indications for GIST, generic manufacturers were able to carve out the non-patented indications by using a skinny label.[66] Accordingly, the first generic versions of imatinib became available in February of 2016, almost six years before the expiration of the '335 patent.[67]

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[58] US Patent No. 6,958,335.

[59] Bryan S. Walsh et al., *Indication-Specific Generic Uptake of Imatinib Demonstrates the Impact of Skinny Labeling*, 40 J. Clinical Oncology 1102, 1102 (2022).

[60] *Id.*

[61] U-649 is the use code for "A method for treating a tumor disease." The Orange Book, 2022, *supra* note 25, at 1632; U.S. Patent No. 6,894,051 for Novartis listed under NDA 021335. *See* U.S. Food & Drug Admin., Approved Drug Products with Therapeutic Equivalence Evaluations 1249 (38th ed. 2018) [hereinafter The Orange Book, 2018].

[62] U-1883 is the use code for "Treatment of gastrointestinal stromal tumors (GIST)." The Orange Book, 2022, *supra* note 25, at 1671. U.S. Patent No. 6,958,335 for Novartis listed under NDA 021335 and NDA 021588. *See* The Orange Book, 2018, *supra* note 61, at 1249-50.

[63] U-791 is the use code for "Gleevec is also indicated for the treatment of patients with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)." The Orange Book, 2022, *supra* note 25, at 1637.

[64] The Orange Book, 2018, *supra* note 61, at 1249-50.

[65] *Id.*

[66] Walsh et al., *supra* note 59, at 1103.

[67] *Id.*

In 2016, the FDA instituted regulations to help clarify "overbroad or ambiguous use codes that may delay approval of generic drugs."[68] Specifically, brand firms must identify and defend the method patents that are associated with the indications approved for its prescription drugs.[69]

The Orange Book allows only a 240-character description for the "use code."[70] These use codes, however, do not always match up identically with the patent claims.[71] Litigation invariably arises out of this ambiguity.[72] To address this issue, the FDA now requires that "the NDA holder's description of the patented method of use…must describe only the approved method(s) of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product."[73] Additionally, the brand firm must "identify with specificity the section(s) and subsections(s) of the approved labeling that describes the method(s) of use claimed by the patent submitted."[74] Courts, however, are still left to interpret if the ambiguous term "could reasonably be asserted."[75]

Also in the 2016 regulations, the FDA created a process for third parties to dispute the accuracy or relevance of a patent listing or use code by providing notice to the agency.[76] The FDA will then send this notice to the brand firm, who has 30 days to confirm the correctness of the patent information with a signed verification or withdraw or amend the listing.[77] The brand firm must also provide a narrative description with no more than 250 words "of the NDA holder's interpretation of the scope of the patent that explains why the existing or amended 'Use Code' describes only the specific approved method of use claimed by the patent for which a claim

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[68] Abbreviated New Drug Applications and 505(b)(2) Applications, 81 Fed. Reg. 69580 (Oct. 6, 2016) (to be codified at 21 C.F.R. pts. 314, 320).

[69] D'Amore, Keane & Doyle, *supra* note 35, at 10.

[70] *Id.*

[71] *Id.* at 10-11.

[72] *Id.* at 11 (referencing as examples *Caraco Pharm*, 566 U.S. 399 (2012); Hospira, Inc. v. Burwell, 2014 U.S. Dist. LEXIS 123972 (2014)).

[73] *Id.* (quoting 21 C.F.R. § 314.53(b)(1)).

[74] *Id.*

[75] *Id.* (quoting 81 Fed. Reg. 69580, 69581).

[76] *Id.* (referencing 21 C.F.R. § 314.53(f)).

[77] *Id.* (referencing 21 C.F.R. § 314.53(f)(1)(i)(A)).

of patent infringement could reasonably be asserted."[78] The brand's response will then be sent to the challenger and posted onto the FDA's website.[79]

Importantly the FDA does not independently review or evaluate the veracity of the brands firm's response.[80] This is consistent with FDA interpretation of its role in listing patent information as "purely ministerial" and that it "lacks both the resources and the expertise to police the correctness…of every patent listing submitted by an NDA holder."[81]

The use of FDA use codes has increased over the past two decades. In 1988, the Orange Book listed 340 unique patents and 61 distinct use codes, for an average of 0.18 use codes per patent.[82] By 2019, there were 7,919 use codes listed for 4,790 unique patents, or 1.65 codes per patent on average.[83] Between 1988 and 2019, the number of use codes per patent thus increased over ninefold.[84]

D. Induced Infringement & Skinny Labeling

Brand firms may be creating large patent thickets to generate a large number of patent use codes. Although each patent can be associated with any number of use codes, it may be advantageous to separate different patents into families with different use codes. This is because if one patent family is invalidated, brand firms can rely on a second patent family to sue based on the method of uses.[85]

The general rule is that the generic drug label must be the same as the brand's drug label.[86] One exception to this rule is if the brand-name drug is approved

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[78] *Id.* (quoting 21 C.F.R. § 314.53(f)(1)(i)(B)).

[79] *Id.*. (referencing 21 C.F.R. § 314.53(f)(1)(iii)).

[80] *Id.* (referencing 21 C.F.R. § 314.53(f)(1)(i)(B)(1)).

[81] *aaiPharma*, 296 F.3d at 237 (noting that the FDA does not substantively review the correctness of the patent information before publication); *see also Leavitt*, 548 F.3d at 106 ("FDA operates in a purely ministerial role"); *Am. Bioscience*, 269 F.3d at 1084 ("FDA [...] administers the Hatch-Waxman Amendments in a ministerial fashion"); 21 C.F.R. § 314.53(e) (2022); 68 Fed. Reg. 36,683 ("[O]ur patent listing role remains ministerial.").

[82] *See* Amicus Curiae Brief of 42 Professors at 9, Teva Pharm. USA, Inc. v. GlaxoSmithKline LLC, No. 22-37 (U.S. Aug. 10, 2022) [hereinafter Brief of 42 Professors], https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4186947.

[83] *Id.*

[84] *Id.*

[85] *See, e.g.*, Kearns v. Gen. Motors Corp., 94 F.3d 1553, 1555 (Fed. Cir. 1996) ("Each patent asserted raises an independent and distinct cause of action.").

[86] 21 U.S.C. § 355(j)(2)(A)(v).

for more than one use that is protected by separate patents or exclusivities.[87] In that case, generic drugs can omit the protected use from its labeling. In this way, the FDA may approve the generic drug for the use that is not protected by patents or exclusivities, so long as removal of the information does not diminish the information needed for safe use of the drug.[88] Brand manufacturers can obtain multiple patents and multiple FDA approvals for the same drug directed to different uses.[89] Each new "use patent" could be tied to a new indication, such as using the drug in a new patient population or to treat a different disease.[90]

Problems arise, however, when the primary patents expire while the secondary use patents are still unexpired and active. This is problematic because a generic company should be able to enter the market when the primary patents for the initial indication expire. Otherwise, brand firms would be able to extend their monopoly indefinitely by simply patenting new indications for their old drugs.

Congress recognized this issue and created a new generic approval pathway called "skinny labeling."[91] Skinny labeling allows generic manufacturers to seek approval for only the unpatented uses of the drug.[92] Generic manufacturers can "carve out" those uses for which there is no patent protection.[93] In sum, the FDA will approve an Abbreviated New Drug Application (ANDA) with a section viii statement only if (1) there is no overlap between the proposed label submitted by the ANDA applicant and the described use in the Orange Book, and (2) removing the information pertaining to the patented method of use from the label does not render the drug less safe or effective.[94]

These labeling issues are important because a generic company's drug label could result in "induced patent infringement."[95] In the pharmaceutical context,

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[87] 21 U.S.C. § 355(j)(2)(A)(viii).

[88] *Id.*

[89] *See, e.g.*, Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 132 S. Ct. 1670, 1676 (2012) (noting "different varieties" of patents on drugs).

[90] 21 U.S.C. § 355(j)(2)(A)(viii).

[91] *See id.*

[92] *See id.*

[93] 21 U.S.C. § 355(j)(2)(A)(viii); *see also* AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1046 (Fed. Cir. 2010); Bayer Schering Pharma AG v. Lupin, Ltd., 676 F.3d 1316, 1318 (Fed. Cir. 2010).

[94] 21 C.F.R. § 314.127(a)(7); *see also*, Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676 and 36,681 (June 18, 2003).

[95] 35 U.S.C. § 271(b).

induced patent infringement requires: (1) a direct infringer (someone who practices the method claimed in the patent), (2) that the defendant *knowingly* induced infringement, and (3) that the defendant possessed the *intent* to encourage another's infringement.[96]

In the pharmaceutical context, a generic manufacturer may be liable for induced infringement of a patented method claim even where the FDA has not approved the generic product for use in accordance with the patented method.

E. The Current State of Skinny Label Litigation

Skinny labels have saved consumers billions of dollars by allowing generics earlier market entry.[97] Between 2015 and 2019, 43% of new generic drugs with multiple indications on their labels employed skinny labeling to avoid unexpired patented method of use claims.[98] Earlier entry has also likely saved consumers billions of dollars.[99] For biosimilars, skinny labels have led to an earlier market entry of 2.5 years with an estimated Medicare savings of $1.5 billion.[100]

This decades-long framework for skinny labeling carve outs has recently been put in jeopardy. The *GSK I* and *GSK II* cases set the stage for brand firms to prevent generics from entering the market using labeling.[101] By overturning the district court's decision, the Federal Circuit found that Teva, the generic manufacturer, induced infringement of GSK's patents.[102] The Federal Circuit found that the skinny label carve outs did not save Teva from liability.[103]

First in 2018, then district court Judge Stark, overturned a $235 million jury verdict finding that Teva induced infringement.[104] In reversing the jury verdict,

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[96] *Id.* (emphasis added); *see also* MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp., 420 F.3d 1369, 1378 (Fed. Cir. 2005).

[97] *See* Bryan S. Walsh et al., *Frequency of First Generic Drug Approvals With "Skinny Labels" in the United States*, 181 J. Am. Med. Ass'n Internal Med. 995 (2021).

[98] *See* Walsh et al., *supra* note 97, at 995; *see also* Alexander C. Egilman et al., *Frequency of Approval and Marketing of Biosimilars with a Skinny Label and Associated Medicare Savings*, 181 J. Am. Med. Ass'n Internal Med. 82 (2023).

[99] Walsh et al., *supra* note 97, at 995 tbl.

[100] Egilman et al., *supra* note 98, at 82.

[101] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc. (*GSK I*), 313 F. Supp. 3d 582 (D. Del. 2018), *rev'd*, 976 F.3d 1347 (Fed. Cir. 2020); *GSK II*, 7 F.4th 1320 (Fed. Cir. 2021).

[102] *GSK I*, 976 F.3d 1347, 1355-57 (Fed. Cir. 2020); *GSK II*, 7 F.4th at 1326.

[103] *GSK II*, 7 F.4th at 1335.

[104] *GSK I*, 313 F. Supp. 3d at 591.

Judge Stark held that "the jury could not reasonably find that Teva caused doctors to infringe."[105] The court also found that there was "no direct evidence…that any doctor was ever induced to infringe the [GSK] patent by Teva's label (either skinny or full).[106] There was no direct evidence that Teva's label caused even a single doctor to prescribe generic [drugs] to a patient to treat [the patent protected indication]."[107]

In October of 2020, the Federal Circuit reversed the district court opinion and held that Teva induced physicians to prescribe a drug for an indication that had been carved out through Teva's skinny label.[108] The Federal Circuit then reinstated a $235 million jury verdict that was initially overturned by the district court judge.[109]

Criticism of the decision, including criticism from Henry Waxman (one of the sponsors of the Hatch-Waxman Act), led the Federal Circuit to reconsider the case in August of 2021.[110] The 2021 decision simply reaffirmed its 2020 decision,[111] and in 2022 the Federal Circuit denied the en banc request to rehear the case.[112]

In its 2021 opinion, the court found that Teva had not adequately removed the carved-out indication from their skinny label.[113] Specifically, the court found that Teva's labeling retained references to clinical trials, instructions for dosing and administration, and indications that could suggest or encourage physicians to prescribe the drug for the carved-out indication.[114] Additionally, the court found that a press release stated the drug was "AB-rated" which can lead to automatic substitution at the pharmacy.[115] Finally, the court found that GSK showed that Teva

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[105] *Id.* at 589

[106] *Id.* at 595

[107] *Id.*

[108] *Id.* at 1355-57 (Fed. Cir. 2020).

[109] *Id.* at 1355-56

[110] *Rehearing Confirms Induced Infringement Liability Despite Skinny Label*, Cooley (Aug. 17, 2021), https://www.cooley.com/news/insight/2021/2021-08-17-gsk-v-teva-federal-circuit-opinion-rehearing-induced-infringement-liability-skinny-label.

[111] *Id.*

[112] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc. (*GSK III*), 25 F.4th 949, 950 (Fed. Cir. 2022) (en banc certiorari denied).

[113] *GSK II*, 7 F.4th at 1326.

[114] *Id.* at 1328-31.

[115] *Id.* at 1324

amended its labeling four years before the remaining patent protection expired to include the previously excluded indications.[116]

This case represents a sea change when it comes to skinny labeling. Judge Prost, in dissent, stated "[n]ow, no skinny-label generic is safe" and "because most skinny labels contain language that (with clever expert testimony) could be pieced together to satisfy a patent claim, essentially all of these cases will now go to trial."[117] Finally, Judge Prost states that:

> [T]he panel majority's decision doesn't just eliminate a generic's ability to depend on the skinny-label system; it also gives brands a powerful tactic: neglect to identify language as patent-covered, then sue a generic for including that very language. Ultimately, if playing by the skinny-label rules doesn't give generics some security from label-based liability, generics simply won't play. And who could blame them? The risk is too great.[118]

Teva has now asked the Supreme Court to review the case.[119]

II
Amarin v. Hikma

Post-*GSK*, brand firms now have a new tool to delay generic entry. Brand firms will likely engage generic manufacturers in a two-step strategy for litigation. The first wave of litigation will be the stereotypical Paragraph IV ANDA litigation. The second wave of litigation will be based on the FDA required labeling. The *Amarin I* and *Amarin II*[120] cases will likely be a prototype for future litigation based on this

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[116] *Id.* at 1325.

[117] *Id.* at 955.

[118] *Id.*

[119] Blake Brittain, *Teva takes $235 mln 'skinny label' dispute with GSK to U.S. Supreme Court*, Reuters (July 14, 2022, 12:24 PM EDT), https://www.reuters.com/legal/government/teva-takes-235-mln-skinny-label-dispute-with-gsk-us-supreme-court-2022-07-13/.

[120] After losing the labeling battle, a group made largely of Amarin shareholders asked the Supreme Court to override the invalidation of the patents claiming that both the Nevada federal judge and the Federal Circuit allowed fraud within the case. See Petition for a Writ of Certiorari at *i, Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., No. 20-1119 (U.S. Feb. 11, 2021). This final attempt to revive the case by an intervenor plaintiff EPA Drug Initiative II (EPADI) was denied for lack of standing both at the district court and the Federal Circuit. *See* Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., No. 2:16-cv-02525-MMD-NJK, 2021 WL 1722896 (D. Nev. Apr. 30, 2021), *aff'd sub nom.* No. 2021-2024, 2022 WL 456912 (Fed. Cir. Feb. 15, 2022) ("Because the Motion is untimely, EPADI was not a party to this case and lacks a

two-step process. However, depending on how broadly courts interpret the *GSK II* ruling, this litigation may delay or deter generics from entering the market.

Amarin's attempt to prevent generic competition came in two waves. In the first wave, Amarin lost its patents in an ANDA Paragraph IV litigation in a Nevada district court.[121] In an attempt to keep its exclusive rights, Amarin then moved venues to bring an induced infringement, in a Delaware court, based on the skinny label.[122]

The first stage was an attempt to sue for patent infringement in an ANDA litigation. Amarin lost this stage when a court invalidated all Amarin's relevant patent claims.[123] The second stage was based on "skinny" labeling. Amarin claimed that Hikma induced infringement of a second set of Amarin's patents because of Hikma's public statements and Hikma's product label.[124] Amarin was again unsuccessful in its labeling arguments as the district court dismissed the case.[125]

Although Amarin was unsuccessful in its bid to prevent the generic company from entering the market, these lawsuits increase the potential costs for competitors to enter the market or delay the entry of these valuable generics. So why would a pharmaceutical firm file a frivolous lawsuit? Vascepa's net sales were roughly $580 million in 2021.[126] Thus, even just a one-week delay would generate $11.2 million for Amarin.

A. Amarin's NDA & Hikma's ANDA

Amarin is the brand manufacturer for the drug Vascepa, a highly purified preparation of EPA (eicosapentaenoic acid), also known as icosapent ethyl.[127] Vascepa is used to treat severe hypertriglyceridemia (HTG), which is a condition

sufficiently protectable interest in it, and as further explained below, the Court will deny EPADI's Motion, and accordingly deny the motion to vacate as well."). This study does not examine the shareholder attempt to invalidate the ANDA judgment.

[121] *Amarin I*, 449 F. Supp. 3d at 971.

[122] *See Amarin II*, 578 F. Supp. 3d at 644.

[123] *Amarin I*, 449 F. Supp. 3d at 971.

[124] *Amarin II*, 578 F. Supp. 3d at 644-45.

[125] *Id.* at 648.

[126] *Amarin Reports Fourth Quarter and Full Year 2021 Financial Results and Provides Business Update*, *supra* note 1.

[127] *Amarin I*, 449 F. Supp. 3d at 973.

in which a patient's fasting triglycerides (TG) rise to very high levels (equal to or over 500 mg/dL).[128] Treating severe HTG patients with Vascepa reduces TGs without increasing low-density lipoprotein cholesterol ("LDL-C" also known as the "bad" cholesterol).[129] Vascepa also can reduce cardiovascular risk in severely hypertriglyceridemic patients on top of a statin, which is the only known treatment shown to confer such a benefit.[130] Thus, Vascepa offers benefits other known treatments cannot in the treatment for severe HTG.

The FDA first approved Vascepa in July 2012 as "an adjunct to diet to reduce triglyceride ("TG") levels in adult patients with severe ($\geq$500 mg/dL) hypertriglyceridemia.[131] The dosage of Vascepa is a 1 gram soft-gelatin capsule, with a daily dose of 4 grams per day taken as two 1 gram capsules twice daily with food.[132] Appendix 1 is a list of patents and expiration dates associated with Vascepa's NDA.[133] Additionally, Appendix 2 contains a list of present and past use codes associated with Vascepa.

In marketing its generic version of Vascepa, Hikma (as required by law) applied the same labeling as Vascepa, which was only approved for severe hypertriglyceridemia at the time of Hikma's ANDA filing.[134] Specifically, Hikma's label states that the product is to be used "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ($\geq$500 mg/dL) hypertriglyceridemia."[135] The dosage of Hikma's product is identical to Vascepa. After Hikma's ANDA filing, however, Amarin was able to acquire "FDA approval for a second indication for Vacepa—reducing the risk of adverse cardiovascular events."[136]

As shown in Appendix 1, Vascepa's product is currently associated with 67 patents.[137] These patents' expiration dates range from May 31, 2027, to June 28,

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[128] *Id.* at 972

[129] *Id.* at 973.

[130] *Id.*

[131] *Id.* at 973-74.

[132] *Id.* at 974.

[133] Orange Book Product Details for NDA N202057, Vascepa (icosapent ethyl) (500mg and 1gm) https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=202057#49 (visited July 21, 2022).

[134] *Amarin I*, 449 F. Supp. 3d at 974.

[135] *Id.* at 975 (quoting Hikma ANDA Application No. A209457).

[136] *Id.* at 974.

[137] Orange Book Product Details for NDA N202057, *supra* note 133.

2033. Additionally, these 67 patents are associated with 69 use codes (40 unique use codes). Appendix 2 contains the descriptions of each use code. It is worth repeating that the FDA does not check the substance of any of these patents or the associated uses. The FDA relies on the drug sponsor to honestly and accurately report patents associated with each drug.

B. Amarin's Patents & ANDA Litigation Loss

As described in Section I(B), when a generic wishes to enter the market before the brand firm's patents expire, they commonly file a "Paragraph IV" certification.[138] Under the Hatch-Waxman Act a Paragraph IV certification states that "[the] patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted."[139] Thus, in July 2016, after Vacepa's initial period of exclusivity expired, Hikma filed an ANDA seeking FDA approval to market a generic version of Vascepa.[140] In a Paragraph IV certification, Hikma argued that Amarin's relevant patents were either invalid or non-infringed.[141]

Hikma's Paragraph IV certification attacked Amarin's U.S. Patent Nos.: 8,293,728 (the '728 patent); 8,318,715 (the '715 patent); 8,357,677 (the '677 patent); 8,367,652 (the '652 patent); 8,431,560 (the '560 patent); and 8,518,929 (the '929 patent).[142] Each of the patents share the same title, "Methods of Treating Hypertriglyceridemia" and are continuations of U.S. Patent No. 8,293,727 (the '727 patent) filed on February 9, 2010. Importantly, each of these patents share identical or near identical specifications.

In the ANDA litigation, the Nevada district court found that all Amarin's relevant patent claims were invalid because they were obviously over the prior art.[143] Specifically, the court found that the prior art "Lovaza PDR [(Physician's Desk Reference)] disclosed a commercially-available preparation of EPA and DHA

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[138] Hemphill & Sampat, *supra* note 45, at 624 (Figure 4, showing that 299 out of 692 drugs were subjected to Paragraph IV challenges).

[139] 21 U.S.C. §§ 355(b)(2)(A)(iv), (j)(2)(A)(vii)(I)–(IV). This is commonly referred to as a "Paragraph IV" certification.

[140] *Amarin I*, 449 F. Supp. 3d at 974 (stating that "[o]n or about July 26, 2016 Hikma…submitted to FDA an ANDA (ANDA No. 209457) with paragraph IV certifications").

[141] *See id.* at 974-75 (referencing Hikma ANDA Application).

[142] *Id.*

[143] *Id.* at 998

[(docosahexaenoic acid)]."[144] The reference states that "Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (>500 mg/dl) triglyceride levels."[145] The difference between the Lovaza reference and Amarin's patent claims was that Lovaza uses both EPA and DHA, while Amarin's patents use "purified EPA, but substantially no DHA."[146]

The Lovaza reference warned that the method of treatment could increase the patient's LDL-C levels.[147] However, a second reference, Mori, taught that DHA increased LDL-C levels, while purified EPA reduced triglycerides without increasing LDL-C.[148] Several other references also "taught that EPA did not increase LDL-C levels."[149] "[T]he Court [found] that a skilled artisan would have wanted to know which active ingredient in Lovaza—EPA or DHA—was responsible for the LDL-C increase (if not both)."[150] The court also found that the Mori reference addressed that exact issue, finding that it was the DHA and not the EPA that increased the LDL-C levels.[151]

Because increases in LDL-C levels could be attributed to DHA and not EPA, the court found that it would have been obvious for a person of ordinary skill in the art to treat patients suffering from severe HTG with purified EPA alone without DHA.[152] Accordingly, the district court found prima facie obviousness had been satisfied to invalidate the patents.[153] After weighing secondary considerations, the

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[144] *Id.* at 985

[145] *Id.*

[146] *Id.* at 992

[147] *Id.* at 992-93

[148] *Id.* at 993 (referencing Mori, et al., *Purified Eicosapentaenoic and Docosahexaenoic Acids Have Differential Effects on Serum Lipids and Lipoproteins, LDL Particle Size, Glucose, and Insulin in Mildly Hyperlipidemic Men*, 71 Am. J. Clinical Nutrition 1085-94 (2000)).

[149] *Amarin I*, 449 F. Supp. 3d at 993 (referencing Hayashi, et al., *Decreases in Plasma Lipid Content and Thrombotic Activity by Ethyl Icosapentate Purified from Fish Oils*, 56 Current Therapeutic Rsch. 24-31 (1995) *and* Kurabayashi, et al., *Eicosapentaenoic Acid Effect on Hyperlipidemia in Menopausal Japanese Women*, 96 Obstetrics Gynecology 521-8 (2000)).

[150] *Amarin I*, 449 F. Supp. 3d at 1007.

[151] *Id.*

[152] *Id.* at 1008-09.

[153] *Id.* at 1009.

court invalidated the patents as obvious.[154] The Federal Circuit later affirmed this ruling.[155]

The Hatch-Waxman Act works by allowing generics to challenge patents to come onto the market earlier, thus dramatically reducing prices for consumers.[156] If the *Amarin v. Hikma* story ended here, it would be a Hatch-Waxman success story. These erroneously granted patents prevented competition and cost consumers billions of added dollars while also harming patient welfare. By invalidating these patents, Hikma provided a service to American consumers. Unfortunately, this was only the first chapter in the *Amarin v. Hikma* story.

C. Amarin's Skinny Label Loss

The second chapter of the *Amarin v. Hikma* story revolves around skinny labeling and the FDA patent use codes. After losing the ANDA litigation in March 2020, Hikma launched its generic product in early November 2020.[157] However, armed with a second wave of new use patents, Amarin sued Hikma on November 30, 2020, for induced infringement on the methods of using Vascepa for the CV indication.[158] Specifically, Amarin alleged that Hikma's skinny label and website press releases induced doctors to infringe these patents.[159] At its heart, this skinny label lawsuit was a second bite at the apple filed with a different legal theory in a different legal forum.[160]

How was Amarin able to employ this strategy? From July 26, 2012, to December 12, 2019, the sole indication for Vascepa was treatment of severe

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[154] *Id.* at 1014-15.

[155] Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., 819 Fed. Appx. 932 (Fed. Cir. 2020) (Rule 36 affirmance).

[156] *See* Aaron S. Kesselheim, Jerry Avorn & Arneet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 J. Am. Med. Ass'n 858, 861 (2016).

[157] Press Release, Hikma Pharm. PLC, Hikma Launches Icosapent Ethyl Capsules (Nov. 5, 2020), https://www.hikma.com/newsroom/article-i4928-hikma-launches-icosapent-ethyl-capsules/.

[158] *Amarin II*, 578 F. Supp. 3d at 643.

[159] Complaint at 92, 100-01, Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., 578 F. Supp. 3d 642 (D. Del. 2022) (No. 1:20-cv-01630) [hereinafter Amarin Complaint]; *see also* Defendants' Opening Brief in Support of Motion to Dismiss at 2, Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., 578 F. Supp. 3d 642 (D. Del. 2022) (No. 1:20-cv-01630) [hereinafter Hikma Defendants' Brief].

[160] The original ANDA case was filed in a Nevada district court. This second skinny label suit was filed in Delaware.

HTG (the "SHTG indication").[161] Thus, when Hikma filed the original ANDA, SHTG was the only indication for Vascepa. However, on December 13, 2019, the FDA approved Vascepa for the treatment of cardiovascular disease (the "CV indication").[162] Amarin was able to exploit a second wave of patents associated with new use codes to argue induced infringement based on Hikma's skinny label and press releases.

The CV indication was protected by a second wave of patents. Specifically, the CV indication patents include U.S. Patent Nos. 9,700,537 (the '537 patent); 8,642,077 (the '077 patent); and 10,568,861 (the '861 patent).[163] The '537 patent was listed on the Orange Book on January 10, 2020, under the use code U-2707 for the "[u]se of VASCEPA as an adjunct to statin therapy to reduce the occurrence of a cardiovascular event in an adult patient with hypercholesterolemia."[164] The '077 patent was listed on the Orange Book on January 6, 2020, under the use code U-2693 for the "[u]se of VASCEPA to reduce triglycerides in a mixed dyslipidemia adult patient with elevated triglyceride (TG) levels ($\geq$150 mg/dL) and on statin therapy."[165] The '861 patent was listed on the Orange Book on March 20, 2020, under the use code U-2756 for the "[u]se of VASCEPA as an adjunct to statin therapy to reduce the risk of cardiovascular death in an adult patient with established cardiovascular disease."[166]

Hikma argued that their skinny labeled product did not "actively induce infringement of patents covering a carved-out indication…because there can

[161] *See* Amarin Complaint, *supra* note 159, at 55.

[162] *See* Letter from John Sharretts, U.S. Food & Drug Admin., to Alex Giaquinto, Amarin Pharma Inc., Supplement Approval: NDA 202057/S-035 (Dec. 13, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/202057Orig1s035ltr.pdf (approving Vascepa "as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels ($\geq$ 150 mg/dL) and established cardiovascular disease or diabetes mellitus or 2 or more additional risk factors for cardiovascular disease" (bullet points removed)).

[163] *See, e.g.*, U.S. Pat. No. 9,700,537, col. 15, ll. 64–65 (claiming "method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient").

[164] *See* U.S. Food & Drug Admin., *Patent and Exclusivity for: N202057*, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (last visited Jan. 5, 2023) [hereinafter *Patents for N202057*], https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=002&Appl_No=202057&Appl_type=N.

[165] *See id.*

[166] *See id.*

be no inducement based on a generic product label unless it 'encourage[s], recommend[s], or promote[s] infringement.'"[167] Additionally, Hikma noted that "[m]erely describing the infringing use, or knowing of the possibility of infringement, will not suffice [for induced infringement liability]; specific intent and action to induce infringement must be shown."[168] Hikma also noted that not only did they omit the patented CV indication on its label, but they actively discouraged the carved out use in its press release. Specifically, its November 2020 press release stated, "Hikma's product is **not approved** for any other indication for the reference listed drug VASCEPA®."[169]

The Delaware district court found that Hikma's label gave no instructions that their product should be administered for the CV indication.[170] The court discussed labeling issues and public statements. With regards to the labeling, the court found that: (a) Hikma's notice regarding side effects was a warning and not an instruction to use the product for the CV indication, and (b) Hikma's removal of the CV risk reduction limitation was mere silence, and that Hikma did not have a duty to discourage infringing use.[171]

With regard to the press releases, the court also found that although Hikma's press releases might support intent to induce infringement, they do not support actual inducement because there was no inducing act.[172] Specifically, Amarin stated that Hikma's website advertised its product for "hypertriglyceridemia" which is broader than the "severe hypertriglyceridemia" included on the label.[173] The court pointed to the GSK and Gruenthal cases for the proposition that a label that includes both infringing and non-infringing uses does "not specifically encourage

[167] Hikma Defendants' Brief, *supra* note 159, at 2-3 (citing HZNP Meds. LLC v. Actavis Lab'ys. UT, Inc., 940 F.3d 680, 701-02 (Fed. Cir. 2019)).

[168] HZNP Meds. LLC v. Actavis Lab'ys. UT, Inc., 940 F.3d 680, 702 (Fed. Cir. 2019).

[169] Hikma Defendants' Brief, *supra* note 159, at 8 (citing its press release stating "Hikma's product is not approved for any other indication for the reference listed drug VASCEPA®"). (emphasis added) https://www.hikma.com/newsroom/article-i4928-hikma-launches-icosapent-ethyl-capsules.

[170] *Amarin II*, 578 F. Supp. 3d at 646.

[171] *Id.*; *see also* Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp., 785 F.3d 625, 632 n.4 (Fed. Cir. 2015) ("[T]he [brand firm] needs to show that [the generic firm] took affirmative steps to induce, not affirmative steps to make sure others avoid infringement.").

[172] *Amarin II*, 578 F. Supp. 3d at 647 ("Intent alone is not enough; Amarin must plead an inducing act.")

[173] *Id.*

use" of the generic for the patented treatment.[174] The court distinguished Hikma's disclosure that its product was "AB Rated" from the GSK case, because Hikma did not point to Vascepa's patented uses in describing itself as Vascepa's generic equivalent.[175] The court analogized the case to Gruenthal, where the genus of uses includes species of infringing and non-infringing uses, without specifically encouraging the use of the generic for the non-infringing uses.[176]

The Delaware court dismissed Amarin's case against Hikma because the labels did not recommend, encourage, or promote an infringing use.[177] Additionally, although the press releases might have been relevant to show intent to induce infringement, they did not support actual inducement because they did not instruct an infringing use.[178]

III
Amarin Patent Portfolio & Use Codes

Amarin's patent strategy is well-developed and built on a large patent thicket. Vascepa's patent thicket started out in 2013 with only six patents associated with one use code.[179] The earliest patent in this thicket expired on January 27, 2020. In contrast, in 2021 Vascepa's Orange Book patent thicket is associated with 67 patents associated with 40 different use codes.[180] Patents in the 2021 cohort have much later expiration dates, with many patents expiring on June 28, 2033. Additionally, not all Amarin's patent thicket is currently listed in the Orange Book. Amarin currently has a total of 132 patents directed towards various aspects of the product.[181]

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[174] *Id.* ("[E]ven if severe chronic pain includes polyneuropathic pain, it also includes mononeuropathic pain and nociceptive pain. Therefore, the proposed ANDA labels do not specifically encourage use of tapentadol hydrochloride for treatment of polyneuropathic pain." (quoting Grunenthal GMBH v. Alkem Lab'ys Ltd., 919 F.3d 1333, 1339 (Fed. Cir. 2019))).

[175] *Amarin II*, 578 F. Supp. 3d at 647.

[176] *Id.* (citing Grunenthal GMBH v. Alkem Lab'ys Ltd., 919 F.3d 1333, 1339 (Fed. Cir. 2019)).

[177] *Amarin II*, 578 F. Supp. 3d at 646-47.

[178] *Id.* at 647.

[179] The Orange Book, 2013, *supra* note 24 (U.S. Pat. Nos. 8,188,146, 8,293,727, 8,293,728, 8,298,554, 8,314,086, and 8,318,715. Where the '727, '728, '086 and '715 patents all have the U-1287 use code. The '146 patent expires on January 27, 2020; the '554 patent expires on April 29, 2030. All other patents expire on February 9, 2030.).

[180] See Appendix 1 and 2.

[181] USPTO Patent Full-Text and Image database Search (PatPF).

In this section we examine how Amarin was able to develop this patent thicket and we examine the prosecution history associated with the relevant patents used in the skinny labeling case. This study argues that the Amarin '077 patent family would likely have been invalidated based on lack of written description support for the method of use claims, had a challenge to the patents on these grounds been pursued.

A. ANDA Invalidated Patents / Skinny Label Asserted Patents

1. USPTO Patent Prosecution Event Summary

As of July 2022, Amarin has sixty-eight patents listed in the Orange Book for the Vascepa product.[182] Amarin, however, has 132 patents protecting various aspects of EPA, many of which are not listed in the Orange Book. There are only five original patents in this Orange Book patent thicket.[183] Sixty patents in this thicket arise from continuation applications and three come from divisional applications. These patents have four unique first named inventors: Mehar Manku (33 patents); Ian Osterloh (11 patents); Mitsuhiro Yokoyama (2 patents); and Paresh Soni (22 patents).

These Orange Book patents come from five different art units: 1628 (21 patents); 1615 (17 patents); 1629 (12 applications); 1611 (1 patent); and 1626 (17 patents). These patents were examined by nine unique examiners: Marcos Sznaidman (20 patents); Aradhana Sasan (17 patents); James Anderson (1 patent); Kevin Weddington (4 patents); Michael Schmitt (2 patents); Barbara Frazier (1 patent); Kristin Vajda (17 patents); Jennifer Kim (1 patents); and Savitha Rao (5 patents). The earliest filing date was February 9, 2010[184] and the latest filing date was August 12, 2021.[185] The earliest issue date from this thicket was October 23, 2012[186] and the latest issue date was April 12, 2022.[187]

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[182] The Orange Book, 2022, *supra* note 25, at 1396–98.

[183] Original patents are patents that do not have priority documents. These five patents are: US Patent Nos. 8,293,727; 8,298,554; 9,603,826; and 10,668,042.

[184] U.S. Patent No. 8,293,727.

[185] U.S. Pat. No. 11,298,333.

[186] U.S. Pat. No. 8,293,727.

[187] U.S. Pat. No. 11,298,333.

Among Amarin's patents, rejections for obviousness-type double patenting (ODP) were common.[188] Overall, 53% (37 of 68) patents encounter at least one ODP rejection.[189] However, when we look at the most recent patents filed after January 1, 2015, we see that 74% (23 of 31) patents encounter at least one ODP rejection.[190] These data suggest that as time progresses, the patent portfolio is increasing, but filling up with more secondary follow-on type patents.

2. FDA Event Summary

Amarin started their patent portfolio with patents directed almost exclusively to the use code U-1287, which corresponds to "methods of reducing [triglyceride] levels in patients suffering from severe hypertriglyceridemia."[191] In fact, all six patents that were asserted in the ANDA litigation were only directed to the U-1287 use code.[192] Table 1 summarizes the patents and use codes associated with the patents asserted in the ANDA litigation.[193] Furthermore, as shown in Figure 1, all parent and child patents of the ANDA litigated patents were directed to the U-1287 use code.

[188] To determine these statistics, we obtained records of patent applications for LexisNexis's Patent Advisor service. *See Bring Predictability and Productivity to Your Patent Prosecution Process With LexisNexis PatentAdvisor*, LexisNexis (last visited Jan. 5, 2023), https://www.lexisnexisip.com/solutions/patent-prosecution/patentadvisor/. Patent Advisor identifies, for each patent application, whether it has received an ODP rejection at some point during prosecution.

[189] *See, e.g.*, Non-Final Rejection *in* U.S. Patent Application No. 12/702,889 (June 20, 2011).

[190] *See, e.g.*, Final Rejection *in* U.S. Patent Application No. 16/775,521 (Sept. 1, 2020).

[191] U.S. Food Drug Admin., Approved Drug Products with Therapeutic Equivalence Evaluations: Orange Book (33rd ed. 2013) (U.S. Pat. Nos. 8,188,146, 8,293,727 8,293,728, 8,298,554, 8,314,086, and 8,318,715. Where the '727, '728, '086, and '715 patents all have the U-1287 use code).

[192] *See* Amarin Pharma v. Hikma Pharms. United States, 449 F.Supp. 3d 967, 971 (2020) (identifying litigated patents); The Orange Book, 2018, *supra* note 61, at ADA123 (noting use codes for patents).

[193] The table is based on data from the FDA's online Orange Book database. *See Patents for N202057*, *supra* note 164.

TABLE 1
PATENTS AND USE CODES INVOLVED IN ANDA LITIGATION

Patent No.	Litigation	Use Code	Patent Expiration Date	FDA Submission Date
8,293,728	ANDA	U-1287	2/9/2030	6/26/2017
8,318,715	ANDA	U-1287	2/9/2030	6/26/2017
8,431,560	ANDA	U-1287	2/9/2030	
8,518,929	ANDA	U-1287	2/9/2030	
8,357,677	ANDA	U-1287	2/9/2030	6/26/2017
8,367,652	ANDA	U-1287	2/9/2030	6/26/2017
8,642,077	Skinny Label	U-2693	4/29/2030	1/6/2020
10,568,861	Skinny Label	U-2756	6/28/2033	3/20/2020
9,700,537	Skinny Label	U-2707	5/31/2027	1/10/2020

FIGURE 1
PATENTS INVALIDATED IN ANDA LITIGATION (IN BOLD) AND RELATED PATENTS

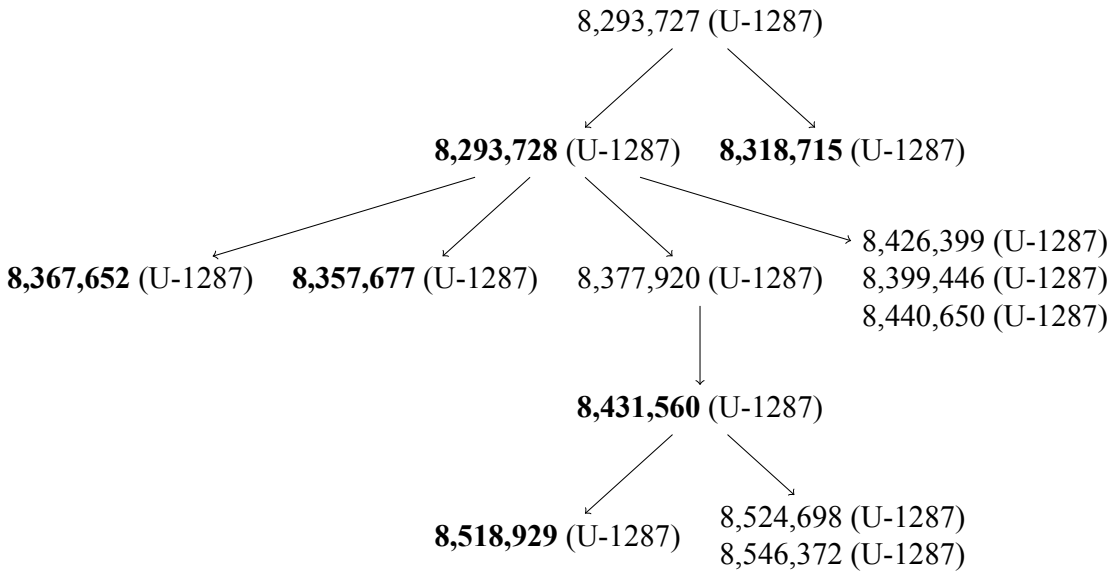


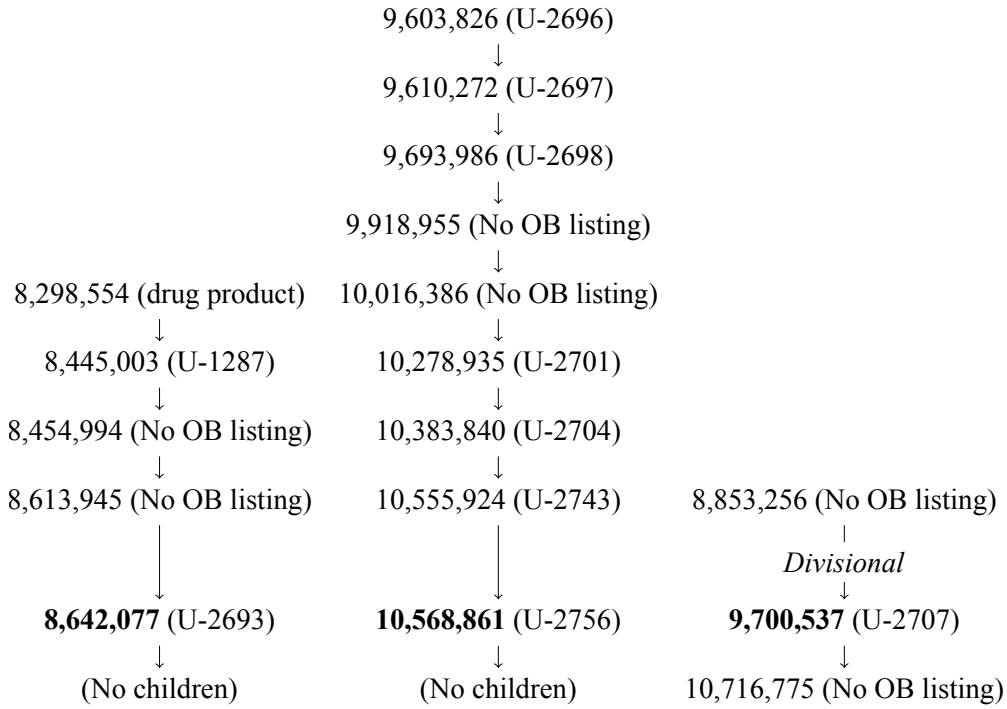
Figure 1 highlights the patent family for the patents that were invalidated (in bold). Most patents that were challenged in the ANDA litigation claimed priority to U.S. Patents Nos. 8,293,727 (the '727 patent), 8,293,728 (the '728 patent) and 8,377,920 (the '920 patent).[194] All patents in the family have the same use code (U-

[194] *See, e.g.*, U.S. Patent No. 8,518,929, at col. 1, ll. 4–13 (filed Feb. 25, 2013) (noting priority claim of patent).

1287).[195] Finally, all patents in this family were continuation applications from the parents to the children. This is significant because these continuation applications have almost identical specifications.[196]

Table 1 and Figure 2 highlight the skinny labeled patent family (patents asserted in bold). US Patent Nos. 8,642,077 (the '077 patent), 10,568,861 (the '861 patent), and 9,700,537 (the '537 patent) were associated with use codes U-2693, U-2756, and U-2707 respectively. Table 2 designates the definitions associated with the relevant use codes. Both the '077 and '861 patents are continuation applications of several patents. In contrast the '537 is a divisional application of US Patent No. 8,853,256 (the '256 patent). For this study, we focus on the '077 patent family and specifically the relationship between the '077 patent and its parent, US Patent No. 8,445,003 (the '003 patent) (Figure 2, in bold).

FIGURE 2
PATENTS ASSERTED IN SKINNY LABEL LITIGATION (IN BOLD) AND RELATED PATENTS



[195] *See* THE ORANGE BOOK, 2018, *supra* note 61, at ADA123.

[196] *See* Transco Prods. Inc. v. Performance Contracting, Inc., 38 F.3d 551, 555–56 (Fed. Cir. 1994) (noting requirement that continuation applications be "based on the same disclosure as an earlier application").

TABLE 2
USE CODE DESCRIPTIONS

Code	Description
U-1287	METHOD OF REDUCING TG LEVELS IN PATIENT SUFFERING FROM SEVERE HYPERTRIGLYCERIDEMIA
U-2693	USE OF VASCEPA TO REDUCE TRIGLYCERIDES IN A MIXED DYSLIPIDEMIA ADULT PATIENT WITH ELEVATED TRIGLYCERIDE (TG) LEVELS (>= 150 MG/DL) AND ON STATIN THERAPY
U-2756	USE OF VASCEPA AS AN ADJUNCT TO STATIN THERAPY TO REDUCE THE RISK OF CARDIOVASCULAR DEATH IN AN ADULT PATIENT WITH ESTABLISHED CARDIOVASCULAR DISEASE
U-2707	USE OF VASCEPA AS AN ADJUNCT TO STATIN THERAPY TO REDUCE THE OCCURRENCE OF A CARDIOVASCULAR EVENT IN AN ADULT PATIENT WITH HYPERCHOLESTEROLEMIA

B. Obviousness & the Skinny-Label Patents

It is important to understand how Amarin was able to create this patent thicket and how they were able to obtain patents directed to so many different use codes. For this study we will focus on the relationship between the '077 patent used in the skinny label litigation and the patents invalidated in the ADNA litigation. Understanding the relationship between the invalidated ANDA patents and the '077 patent asserted for the skinny label litigation explains why Amarin's skinny label litigation was particularly egregious. Figure 3 details the relationship between the '077 patent and the ANDA invalidated patents.

In sum, the '077 patent[197] is the great-grandchild of the '003 patent. The specifications of the '077 and '003 patents are nearly identical. Amarin filed a terminal disclaimer for the '003 patent linking them to the '728, '715, '677 and '652 patents, which were all invalidated in the ANDA litigation. Additionally, as discussed below, written description support for the use of Vascepa to reduce

[197] *See* U.S. Patent No. 8,642,077. The '077 patent is the great great great grandchild of the 61/173,763 provisional application (the '763 provisional). In fact, the '763 provisional serves as the priority document for 26 other Amarin patents. The first child patent to come out of the '763 provisional was U.S. Patent No. 8,298,544 (the '544 patent). Additionally, the '554 patent has 25 patents that claim priority to the '544 patent. The '554 patent is important because it is currently the only patent directed to a drug product (formulation and composition patents). All other patents were directed towards method of uses.). See also Figure 3 and THE ORANGE BOOK, 2022, *supra* note 25, at 1652, 1703-04, 1706.

triglycerides in a mixed dyslipidemia adult on statin therapy with elevated TG levels is not found in either the '003 or the '077 patents.

The '077 patent was likely filed to prevent Hikma from using its product to treat patients on statin therapy with TG levels equal to or above 150 mg/dL (use code U-2693). However, this patent claimed priority to the '003 patent, which was directed towards a method of reducing TG levels in patients with SHTG (use code U-1287), which relates to Hikma's skinny label carved out U-1287 use.

The key problem with the '077 patent is that the '003 great grandparent used a terminal disclaimer to overcome an anticipated obviousness type double patenting rejection from the examiner. On October 2, 2012, the patent examiner identified "double patenting issues with numerous co-pending cases."[198] Furthermore, obviousness-type double patenting issues were discussed in an October 10, 2012 phone call.[199] In response, the applicant filed 17 terminal disclaimers to "obviate a provisional double patenting rejection over a pending 'reference' application."[200] In explaining the rationale for allowance, the examiner stated that Applicants filed Terminal Disclaimers on 10/22/2012 over the following copending applications, thereby obviating the need for any obviousness-type double patenting rejections, as discussed in the telephonic interview of 10/10/2012.[201]

Filing these terminal disclaimers is important because terminal disclaimers can be an admission that the application is obvious over a prior patent in the same family.[202] In this case, it is relevant that the applicant filed a terminal disclaimer for the '003 patent, which suggests that the '003 patent is obvious in light of the '728, '715, '677, and '652 patents. This is important because all these patents were previously invalidated for obviousness in the ANDA litigation.[203] While the

[198] U.S. Patent Application No. 13/458,496, Applicant Initiated Interview Summary filed Oct. 17, 2012 (filed Apr. 27, 2012).

[199] *Id.*

[200] Seventeen terminal disclaimers were filed on October 22, 2012, using the PTO/SB/25 form which is a "Terminal Disclaimer to Obviate a Provisional Double Patenting Rejection Over a Pending 'Reference' Application."

[201] U.S. Pat. Application No. 13/458,496, Notice of Allowance filed Feb. 1, 2013 (filed Apr. 27, 2012).

[202] *See* Letter from Katherine K. Vidal, U.S. Patent & Trademark Off., to Robert M. Califf, U.S. Food & Drug Admin., at 6 (July 6, 2022), https://www.uspto.gov/sites/default/files/documents/PTO-FDA-nextsteps-7-6-2022.pdf (discussing terminal disclaimers used to overcome obviousness-type double patenting).

[203] *See Amarin I*, 449 F. Supp. 3d 967, 1014 (D. Nev. 2020).

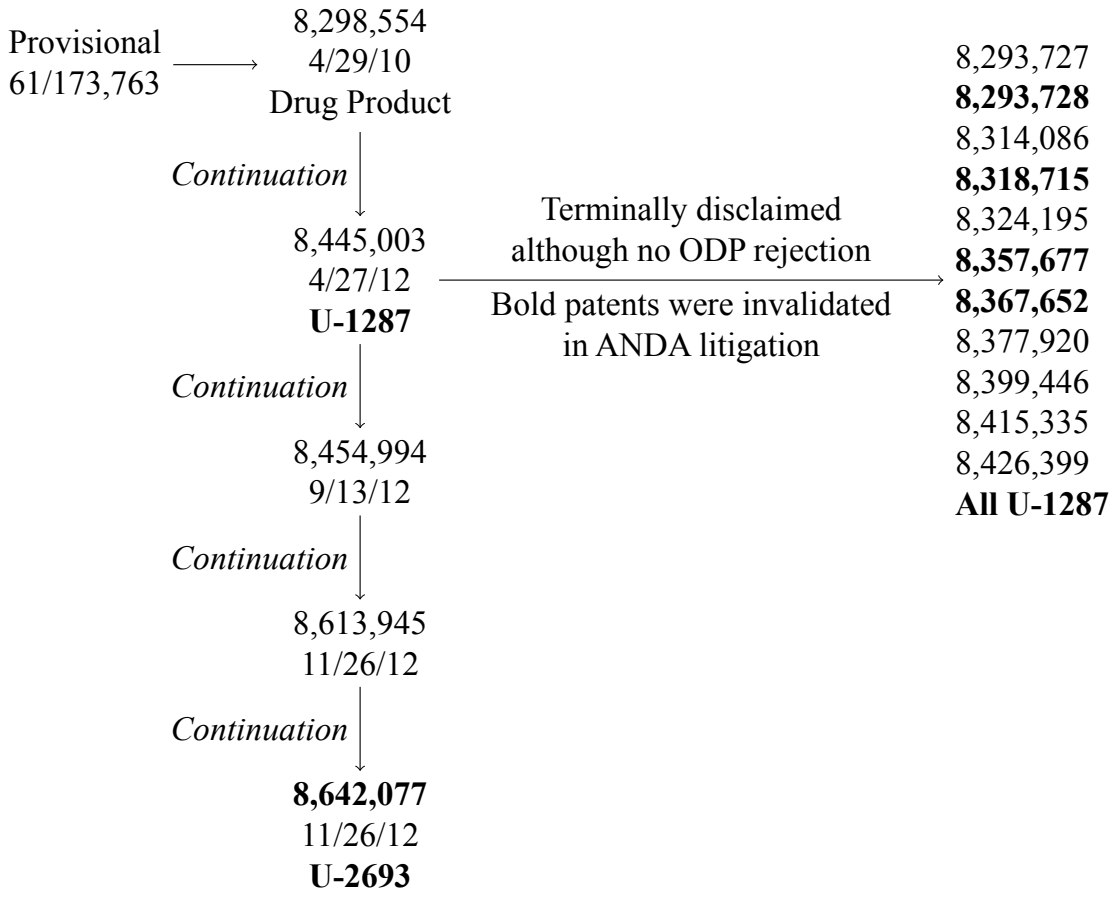
validity of the '003 patent must of course ultimately be determined on their own merits, the close relationship between the '003 patent and the invalidated ANDA-litigation patents suggests, at a minimum, serious questions about the validity of the former.[204]

Interestingly, originally in 2013, Vacepa was listed in the orange book with a "Drug Substance" and "Drug Product" code associated with U.S. Patent No. 8,188,146 (the '146 patent). This patent had the earliest expiration date (January 27, 2020) of the entire Orange Book patent family. Interestingly, the '146 patent discloses the composition of matter but is directed towards the use of Vascepa for psychiatric or central nervous system disorders.[205]

[204] To be sure, there are two forms of "obviousness" at play: The relationship between the '003 patent and the ANDA-litigation patents is based on the judicially created doctrine of obviousness-type double patenting, while the invalidity of the ANDA-litigation patents was premised on obviousness under 35 U.S.C. § 103. Nevertheless, the two doctrines have a relevant relationship. The '003 patent would be invalid for obviousness-type double patenting over an ANDA-litigation patent if the former patent's claims "are obvious over the [latter] patent claims." *In re* Janssen Biotech, Inc., 880 F.3d 1315, 1325 (Fed. Cir. 2018) (quoting *In re* Basell Poliolefine Italia SPA, 547 F.3d 1371, 1376 (Fed. Cir. 1998)). To the extent that the prior art is sufficiently close to the ANDA-litigation patent so as to render that patent obvious under § 103, then the prior art is likely also very close to the '003 patent as well.

[205] U.S. Pat. No. 8,188,146 col. 2, ll. 18–30 (The diseases listed include: "schizophrenia, schizoaffective disorder or a schizotypal disorder; depression or manic-depression (bipolar disorder); anxiety or panic disorder or social phobia, or a sleep disorder or an attention deficit, conduct, hyperactivity or personality disorder; autism; Alzheimer's disease, vascular dementia or another dementia, including multi-infarct dementia, Lewy body disease and diseases attributable to prion disorders; Parkinson's disease, or other motor system disorder; multiple sclerosis; stroke; epilepsy; and Huntington's disease or any other neuro-degenerative disorder.").

FIGURE 3
RELATIONSHIPS BETWEEN THE '077 PATENT AND ANDA LITIGATION PATENTS.



C. Written Description & the Skinny-Label Patents

In addition to the questionable validity of the skinny-label patents in view of obviousness, there are questions about the validity of those patents under the written description requirement of 35 U.S.C. § 112(a). Under that statute, the specification of a patent must "describe the invention sufficiently to convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application."[206] The written description requirement is satisfied if "the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing

[206] LizardTech, Inc. v. Earth Res. Mapping, Inc, 424 F.3d 1336, 1345 (Fed. Cir. 2005); *See also* 35 U.S.C. § 112(a).

date."[207] A sufficient description of a genus requires the specification to disclose "either 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."[208]

In the pharmaceutical and other medical arts, applications claiming new methods of treatment are typically supported by test results.[209] Applicants cannot satisfy the written description requirement by simply presenting a "laundry list" of compositions that might or might not meet the claimed invention.[210] The Supreme Court stated that "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."[211] Similarly, the Federal Circuit has described the task of meeting the written description requirement as being akin to providing "blaze marks which single out particular trees in a forest, rather than simply pointing to trees."[212]

The '077 patent looks in many ways like that forest with no blaze marks. The specification is directed towards stable pharmaceutical compositions of highly pure eicosapentaenoic acid (EPA). The '077 patent discloses huge laundry lists of concentrations; weights of EPA, purity of EPA; capsule shells with specific baseline peroxide values; film-forming material and plasticizer weight ratios; concentration of degradation products; treatment and/or prevention of cardiovascular disease (as defined as a "disorder of the heart or blood vessels or any symptom thereof, or any disease or condition that causes or contributes to a cardiovascular disease" with 57 non-limiting examples); different treatment groups (at least 89 different groups); treatment periods (1 week to 200 weeks); 25 different outcomes (each outcome having about 12 possible ranges); and dosing amounts (1-10,000 mg and 103 different concentrations).

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[207] Ariad Pharms., Inc. v. Eli Lilly Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

[208] *Id.* at 1350.

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

[210] Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336, 1345-46 (Fed. Cir. 2013); Fujikawa v. Wattanasin, 93 F.3d 1559, 1571 (Fed. Cir. 1996); Purdue Pharma L.P. v. Iancu, 767 F. App'x 918, 924 (Fed. Cir. 2019).

[211] Brenner v. Manson, 383 U.S. 519, 536 (1966).

[212] Idenix Pharms. LLC v. Gilead Sci., Inc., 941 F.3d 1149, 1164 (Fed. Cir. 2019) (internal quotation marks omitted).

The specification focuses on a host of different variables, including: (a) EPA amount (50-5000 mg in 102 different possible concentrations)[213]; (b) addition of antioxidants (0.01% to 0.1% or 0.025% to 0.05%)[214]; lack of docosahexenoic acid (DHA)[215]; EPA concentrations (60-100%, with at least 23 different concentrations).[216] The discussion of all of the embodiments of the invention is very general in nature and lacks any disclosure regarding which compositions produce the results set forth in the patents' claim and use code.

The claims of the '077 patent fail the written description requirement on almost every level. Specifically, there are no examples showing how Vascepa is used to reduce triglycerides in patients with mixed dyslipidemia. Mixed dyslipidemia is mentioned three times in the entire specification. The first time mixed dyslipidemia is mentioned is in a laundry list of 57 other indications.[217] The second time mixed dyslipidemia is mentioned is in the framework of a blood lipid therapy.[218] Finally, the '077 patent only states in a conclusory fashion that the invention can treat or prevent mixed dyslipidemia by "administering to the patient one or more compositions as disclosed herein."[219] There are no disclosures regarding which concentrations or formulations are effective. Furthermore, there is no disclosure explaining why patients having triglyceride levels of $\geq$150 mg/dL is relevant. Finally, there is no discussion on why patients need to be on statins therapy. In fact, contradicting the use of statins, the '077 patent discloses that one embodiment of the invention is directed to treatment when a statin is considered inadequate.[220]

The formulation and dosage limitations in the asserted claims of the '077 patent are broad. All the asserted claims recite daily dosages from 2500 mg to 5000 mg.[221] Based on the specification of the '077 patent, it would be difficult to determine which concentrations, which dosage regimens, and which formulations

[213] U.S. Pat. No 8,188,146, col. 3, l. 6-35.
[214] *Id.* at 1. 37-43
[215] *Id.* at 1. 44-55
[216] *Id.* at col. 3-5.
[217] U.S. Pat. No. 8,642,077, col. 15, l. 26-55.
[218] *Id.*, col. 16, l. 7-10.
[219] *Id.* at 1. 1-2.
[220] *Id.* at l. 2-7.
[221] Accordingly, the '077 patent may be invalidated based on the lack of written description support for the claimed ranges. *See* Indivior U.K. Ltd. v. Dr. Reddy's Lab'y, Inc., 18 F.4th 1323, 1328-30 (Fed. Cir. 2021).

would be effective for treating patients with mixed dyslipidemia. Additionally, it is not even clear that all patients with mixed dyslipidemia would benefit from this therapy.[222]

The specification contains a long list of EPA formulations, but does not identify which of these formulations can satisfy the recited functional limitations when administered in the amounts specified in the claims. In fact, there are no examples of administering the drug to any patient. Simply providing lengthy and detailed listings of various excipients and concentrations that can be used to formulate Vascepa does not provide written description support for the asserted method claims.[223] Additionally, the specification does not describe the structural features that might be in common with compositions that would work across the full scope of the claims. In this case, the claims of the patent are broad and there are no operative species disclosed in the specification. Accordingly, the specification of the '077 patent does not identify which formulations would satisfy the recited functional limitations when administered in the specified amount in the claims.[224] To the extent that the '077 patent might pass muster under 35 U.S.C. § 112(a), that suggests that the written description doctrine is failing to sufficiently police these "laundry list" patents of questionable innovative value.[225]

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[222] The '077 patent states that one embodiment of the invention provides "a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate . . ." U.S. Pat. No. 8,642,077, col. 22 l. 3-6 (suggesting that treatment with statins may be ineffective for some patients).

[223] *See* Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336, 1345-46 (Fed. Cir. 2013); Fujikawa v. Wattanasin, 93 F.3d 1559, 1571 (Fed. Cir. 1996); Lipocine Inc. v. Clarus Therapeutics, Inc., 541 F. Supp. 3d 435 (D. Del. 2021).

[224] *See also* Lipocine Inc. v. Clarus Therapeutics, Inc., 541 F. Supp. 3d 435, 462-63 (D. Del. 2021) (showing that the testosterone undecanoate drug patent contained a long list of formulations but failed the written description requirement because the specification did not describe which formulations would produce the claimed results).

[225] In *Union Oil Co. v. Atlantic Richfield Co.*, the Federal Circuit declined to invalidate a patent directed to a composition of gasoline under the written description requirement of § 112. *See* 208 F.3d 989, 1001 (Fed. Cir. 2000). In dissent, Judge Lourie questioned how the written description requirement could be satisfied by a patent claim where the features were scattered throughout and "[o]ne must pick and choose among eight different types of fuel characteristics, broadly described, in order to arrive at any of the claimed combinations." *Id.* at 1004 (Lourie, J., dissenting). Insofar as Judge Lourie was in the minority, *Union Oil* suggests that at least some Federal Circuit judges are willing to read the written description requirement especially generously.

D. The Patent Quality Disconnect

Why was Amarin interested in creating a large patent thicket based on secondary method of use patents of questionable validity? Most likely it was to protect Vascepa's revenues, which have recently been about half a billion dollars a year.[226] These patents likely are used to delay generic market entry. For 2021, with Vascepa as its primary product, Amarin made about $1.59 million a day.[227] The cost of filing a complex biotechnology patent thicket is relatively inexpensive, with an average cost of $11,657 per patent.[228] Additionally, the average cost of a litigation when more than $25 million is at risk is approximately $5.7 million.[229] Thus, building and litigating a complex patent thicket pays for itself with about one or two weeks' worth of sales.

Many commentators have focused on the creation of patent thickets to evergreen patents.[230] Previous studies indicate that patent thickets comprised of "secondary" less innovative patents are the ones that are playing a role in delaying generic entry. Creation of these patent thickets may play an important role in delaying or preventing generics from entering the market. The *Amarin* case study shows that these secondary patents can play a role not only in protecting the product during ANDA litigation but can play a role in a "second wave" of litigation based on drug labeling requirements.

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[226] *See* Amarin Corp., Annual Report (Form 10-K), at F-5 tbl. (Mar. 1, 2022).

[227] *See id.* (noting $580 million in revenues for 2021).

[228] Am. Intell. Prop. L. Ass'n L. Pract. Mgmt. Comm., AIPLA 2021 Report of the Economic Survey I-100 Q40c (2021) (showing that the average cost for a complex biotechnology/chemical utility application is $11657, and the median cost is $10,250); *see also* AIPLA 2021 Report of the Economic Survey I-102 Q40g (2021) (showing that the average amendment/argument for a complex biotechnology/chemical patent is $4,574, and a median cost of $3,500).

[229] *Id.* at I-148 Q45Ao (showing that the average cost of patent infringement litigation (including pre-trial, trial, post-trial and appeal) is $5,768,000 with a median of $4,000,000 when more than $25 million is at risk).

[230] *See* Robin Feldman, *May Your Drug Price be Evergreen*, 5 J.L. & Biosciences 5990 (2018); *see also* Bo Wang, Jun Liu & Aaron S. Kesselheim, *Variations in Time of Market Exclusivity Among Top-Selling Prescription Drugs in the United States*, 175 J. Am. Med. Ass'n Internal Med. 635 (2015).

IV
Policy Solutions

A. The PTO Should Institute Enhanced Review of Orange Book Patents

There are several simple solutions that the PTO could institute that would not require Congressional intervention. First, the PTO could require applicants to identify their patents as potential Orange Book patents so that the PTO could give them to the appropriate examiners. These patents could go to a special art unit that uses team examination with added support. Second, the PTO and FDA should collaborate to verify the information that is submitted to the FDA for Orange Book listing. Third, the PTO should increase the fees associated with serial continuation applications. Finally, the PTO could abolish the use of terminal disclaimers to obviate an obviousness type double patenting rejection.

1. Flag Orange Book Applications for Team Examination

The PTO could play a larger role in preventing these patent thickets from developing. The PTO could require applicants to flag patents that would be listed on the Orange Book in advance. Additionally, the PTO could pay closer attention to those patents in large families that would receive obviousness-type double patenting rejections. Congress could create an FDA reexamination procedure to correct incorrectly granted patents based on clinical information and/or disclosures made by the applicant to the FDA. Finally, the FDA could work in conjunction with the PTO to substantively review the Orange Book listings to make sure that the products and methods listed in the Orange Book match with the claims of the patent.

The PTO could require applicants to flag their patents that would be placed in the Orange Book if the claims were to be issued.[231] These applications would then be sent to an Orange Book art unit that would use three experienced examiners instead of just one examiner. Additionally, one team member should be versed in FDA approval procedures to help flag the relevant information for review.

This new art unit could be given access to specialized tools, such as AI prior art searching. Others have suggested that giving examiners more time could result

[231] Tu & Lemley, *supra* note 19, at 1708-12 (arguing for applicant disclosure of Orange Book patent applications).

in better examination.[232] Although we show that added time will likely not result in better examination, this special art unit could be given extra time as a pilot program to determine if added time results in stronger examination.[233]

Using a team examination approach would cost the PTO slightly more than the single examiner approach. However, this cost would be more than offset by preventing patent thickets, where even one erroneously granted patent has been shown to cost the public over $2 billion in added drug costs.[234]

2. PTO & FDA Collaboration to Verify Orange Book Information

Currently, the FDA does not substantively examine or verify the accuracy of information placed in the Orange book. FDA sees its role in managing the Orange Book as "purely ministerial" and that it "lacks both the resources and the expertise to police the correctness. . . of every patent listing submitted by an NDA holder."[235] The FDA should work in conjunction with the PTO to independently review the information submitted by applicants. The PTO has the expertise to examine and determine if the use codes associated match the claims of the patents. If not, they should not be given the use codes. This simple check would help reduce the patent thickets created by new use codes, which currently go unexamined.

3. Increased Fees & Scrutiny for Late-Stage Continuation Applications

The PTO could also target these patent thickets without legislation. The PTO could create a tiered fees system associated with each additional continuation application. These fees would increase stepwise for each new generation. For example, fees associated with child application would only be 1.5 times the normal fees, while fees associated with grandchildren would be four or five times the normal fees. Maintenance fees associated with these patents should also increase

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[232] Michael D. Frakes & Melissa F. Wasserman, *Irrational Ignorance at the Patent Office*, 72 VAND. L. REV. 975, 981 (2019); Michael D. Frakes & Melissa F. Wasserman, *Investing in Ex Ante Regulation: Evidence from Pharmaceutical Patent Examination* 4–7 (Nat'l Bureau of Econ. Rsch., Working Paper No. 27579, 2020).

[233] Tu & Lemley, *supra* note 19, at 1709-1710.

[234] David Miller et al., *The Costs of Delayed Generic Drug Entry: Evidence from a Controversial Prostate Cancer Drug Patent*, J. GEN. INTERNAL MED. (July 13, 2021) (showing that an inappropriately awarded secondary patent cost consumers $2 billion).

[235] *aaiPharma*, 296 F.3d at 237 (noting that the FDA does not substantively review the correctness of the patent information before publication); *see also Leavitt*, 548 F.3d at 106; *Am. Bioscience*, 269 F.3d at 1084; 21 C.F.R. § 314.53(e) (2022); *see also* 68 Fed. Reg. 36,683.

stepwise with each new patent generation. This would place pressure on applicants to remove fourth or fifth generation patents that may not be adding value but are only used to delay or deter generic market entry.[236] Increasing PTO fees may deter brand firms from filing dozens of follow-on patents to create large thickets that increase competitor transaction costs.

4. Limit Terminal Disclaimers as a Response to Obviousness-Type Double Patenting Rejections

The PTO could apply stricter scrutiny to those continuation applications that come from large patent families to determine if there is something patentably different from other family members. This is especially true if these patent families would receive obviousness type-double patenting rejections and if terminal disclaimers have already been filed for other family members. A group of senators led by Patrick Leahy have suggested the possibility of tying patents together when those patents are linked by terminal disclaimers. They suggest that filing a terminal disclaimer may be considered an admission of obviousness and may make it so that all of these patents would stand and fall together if litigated.[237]

Alternatively, the PTO could impose new limitations on the ability of a terminal disclaimer to overcome an obviousness type-double patenting rejection.[238] With sufficiently effective limitations, applicants would then have to focus on the differences between their current application and their previous patents and show that the claims are non-obvious variations of their previously patented claims.

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[236] One counterpoint is that given the immense value to pharmaceutical companies in even short delays in generic entry, it may be unlikely that higher filing fees will do much to deter abusive filing practices. See Erik Hovenkamp & Stephen C. Salop, *Asymmetric Stakes in Antitrust Litigation* (USC Legal Stud. Rsch. Paper Series No. 20-1, 2020) https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3563843.

[237] *See* Letter from U.S. Senators Patrick Leahy, John Cornyn, Richard Blumenthal, Susan M. Collins, Amy Klobuchar, and Mike Braun to Kathi Vidal, Dir. of U.S. Pat. and Trademark Off. (June 8, 2022).

[238] For existing rules for terminal disclaimers, see generally 37 C.F.R. § 1.321(d). The PTO has been deemed to have authority to impose requirements on the content of terminal disclaimers in order to address policy concerns arising out of obviousness-type double patenting. *See In re* Van Ornum, 686 F.2d 937, 947–48 (C.C.P.A. 1982); Daniel Kazhdan, *Obviousness-Type Double Patenting: Why It Exists and When It Applies*, 53 Akron L. Rev. 1017, 1028 (2019) (noting PTO's rulemaking on content of terminal disclaimers to address "public-rights" issues).

B. Congress Should Take Measures to Stop Patent Thickets

Congress could also procedurally stop patent thickets with new PTO rules. Congress could halt most patent thickets by creating laws that limit the applicant's ability to file a continuation application to within two years of the first office action in the priority application. This would prevent serial continuation applications and would force applicants to focus on only those patents that are most valuable to the applicant. It has previously been shown that most patents that are filed to delay generic entry are "secondary" patents, which are usually based on continuation applications.[239]

Congress could also create a new FDA reexamination process to help increase communication between the PTO and FDA.[240] Directly after FDA approval of the drug, NDA information should be sent to the PTO. The PTO should then review this information to determine if there is a substantial new question of patentability. If there is, then the PTO should reopen prosecution with the patentee to determine if the scope of the claims matches the disclosure and whether evidence found in the clinical trials contradicts the patent claims.

Conclusion

The Hatch-Waxman Act has created a carefully balanced set of incentives to help stimulate innovation in the pharmaceutical industry while also allowing generic manufacturers to enter the market, thereby greatly reducing the prices associated with these drugs. However, increasingly brand pharmaceuticals are using the complex regulatory frameworks of both the FDA and the PTO to extend their monopoly rights.

The patent two-step dance is yet another strategy where brand firms are attempting to extend their monopoly rights. Unfortunately, under *GSK II*, the Federal Circuit has resuscitated this once abandoned strategy. If allowed to stand, this induced infringement strategy based on patent use code thickets might stymie generic competition for years to come. This will lead to increased costs for American patients and the federal government.

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[239] Tu & Lemley, *supra* note 19 (Table 1, showing that 73% of invalidated patents were continuation applications).

[240] S. Sean Tu, *FDA Reexamination: Increased Communication Between the FDA and USPTO to Improve Patent Quality*, 60 U. Hous. L. Rev. (forthcoming in 2022).

The Supreme Court should grant certiorari in the *GSK II* case to correct the confusion that the Federal Circuit has created by overturning a system that has been in place for decades.[241] Additionally, the PTO and FDA should create rules to re-balance the Hatch-Waxman Act to serve its initial purpose, namely balancing pharmaceutical innovation and lowering drug prices.

[241] *See* Brief of 42 Professors, *supra* note 82.

Appendix 1: Patents on Vascepa

Use codes apply to both 500mg and 1000mg drug products unless otherwise specified.

Patent	Exp. Date	Use Codes
8,293,727	2/9/30	U-1287
8,293,728	2/9/30	U-1287
8,298,554	4/29/30	Drug product
8,314,086	2/9/30	U-1287
8,318,715	2/9/30	U-1287
8,357,677	2/9/30	U-1287
8,367,652	2/9/30	U-1287
8,377,920	2/9/30	U-1287
8,399,446	2/9/30	U-1287
8,410,086	6/15/30	U-2688
8,415,335	2/9/30	U-1287
8,426,399	2/9/30	U-1287
8,431,560	2/9/30	U-1287 (1000mg only)
8,440,650	2/9/30	U-1287
8,445,003	4/29/30	U-1287
8,445,013	4/29/30	U-1287
8,454,994	4/29/30	U-2689
8,455,472	6/15/30	U-2690 (1000mg only)
8,501,225	4/29/30	U-1287
8,518,929	2/9/30	U-1287
8,524,698	2/9/30	U-1287
8,546,372	2/9/30	U-1287
8,551,521	4/29/30	U-1287
8,563,608	4/29/30	U-1287
8,617,593	4/29/30	U-1287 (500mg only) U-1478 (1000mg only) U-2691
8,617,594	4/29/30	U-1287
8,618,166	4/29/30	U-2689 (1000mg only)

8,623,406	4/29/30	U-1287 (500mg only) U-1478 (1000mg only) U-2692
8,642,077	4/29/30	U-2693
8,669,245	6/15/30	U-2694
8,680,144	2/9/30	U-2695
8,691,871	4/29/30	U-2689
8,703,185	4/29/30	U-2691
8,709,475	4/29/30	U-2689
8,710,041	6/15/30	U-2690
9,198,892	9/25/27	U-2706
9,603,826	6/28/33	U-2696
9,610,272	6/28/33	U-2697
9,623,001	6/28/33	U-2698
9,693,984	6/28/33	U-2697
9,693,985	6/28/33	U-2696
9,693,986	6/28/33	U-2698
9,700,537	5/31/27	U-2707
9,918,954	6/28/33	U-2699
10,010,517	4/29/30	U-2690
10,265,287	4/29/30	U-2700
10,278,935	6/28/33	U-2701
10,278,936	6/28/33	U-2702
10,278,937	6/28/33	U-2703
10,383,840	6/28/33	U-2704
10,555,924	6/28/33	U-2743
10,555,925	6/28/33	U-2744
10,568,861	6/28/33	U-2756
10,576,054	6/28/33	U-2762
10,668,042	6/28/33	U-2841
10,786,478	6/28/33	U-2959 U-2960
10,792,267	4/29/30	U-2961
10,792,270	6/28/33	U-2962

10,842,766	4/29/30	U-2997
10,842,768	6/15/30	U-2688
10,881,632	4/29/30	U-3052
10,894,028	6/28/33	U-3053
11,000,499	6/28/33	U-3126
11,103,477	4/29/30	U-3209
11,116,742	6/28/33	U-3221
11,154,526	4/29/30	U-3240
11,213,504	4/29/30	U-3292
11,298,333	6/28/33	U-3358

Appendix 2: Vascepa Use Codes

Drug Product

Patents: 8,298,554

U-1287: Method of reducing TG levels in patient suffering from severe hypertriglyceridemia

Patents: 8,293,727, 8,293,728, 8,314,086, 8,318,715, 8,357,677, 8,367,652, 8,377,920, 8,399,446, 8,415,335, 8,426,399, 8,431,560, 8,440,650, 8,445,003, 8,445,013, 8,501,225, 8,518,929, 8,524,698, 8,546,372, 8,551,521, 8,563,608, 8,617,593, 8,617,594, 8,623,406

U-1478: Method of reducing TG levels in patient on statin therapy suffering from severe hypertriglyceridemia

Patents: 8,617,593, 8,623,406

U-2688: Use of Vascepa to lower triglycerides and ldl-c in an adult patient with elevated triglyceride (TG) levels (about 200 mg/dl to less than about 500 mg/dl) and on statin therapy

Patents: 8,410,086, 10,842,768

U-2689: Use of Vascepa to treat mixed dyslipidemia in an adult patient with elevated triglyceride (TG) levels ($\geq$ 150 mg/dl) and on statin therapy

Patents: 8,454,994, 8,618,166, 8,691,871, 8,709,475

U-2690: Use of Vascepa to lower triglycerides in an adult patient with elevated triglyceride (TG) levels (about 200 mg/dl to less than about 500 mg/dl) and on statin therapy

Patents: 8,455,472, 8,710,041, 10,010,517

U-2691: Use of Vascepa to treat hypertriglyceridemia in an adult patient with elevated triglyceride (TG) levels ($\geq$ 150 mg/dl) and on statin therapy

Patents: 8,617,593, 8,703,185

U-2692: Use of Vascepa to reduce triglycerides in an adult patient with elevated triglyceride (TG) levels ($\geq$ 150 mg/dl) and on statin therapy

Patents: 8,623,406

U-2693: Use of Vascepa to reduce triglycerides in a mixed dyslipidemia adult patient with elevated triglyceride (TG) levels ($\geq$ 150 mg/dl) and on statin therapy

Patents: 8,642,077

U-2694: Use of Vascepa to lower triglycerides in a mixed dyslipidemia adult patient with elevated triglyceride (TG) levels (about 200 mg/dl to less than about 500 mg/dl) and on statin therapy

Patents: 8,669,245

U-2695: Use of Vascepa to treat mixed hypertriglyceridemia in an adult patient with elevated triglyceride (TG) levels ($\geq$ 150 mg/dl) and on statin therapy

Patents: 8,680,144

U-2696: Use of Vascepa as an adjunct to statin therapy to reduce the risk of cardiovascular death, coronary revascularization, and unstable angina in an adult patient with elevated triglyceride levels (TG $\geq$ 150 mg/dl to about 500 mg/dl)

Patents: 9,603,826, 9,693,985

U-2697: Use of Vascepa as an adjunct to statin therapy to reduce the risk of cardiovascular death and/or unstable angina in an adult patient with elevated triglyceride levels (TG $\geq$ 150 mg/dl to about 500 mg/dl)

Patents: 9,610,272, 9,693,984

U-2698: Use of Vascepa as an adjunct to statin therapy to reduce the risk of cardiovascular death and/or coronary revascularization in an adult patient with elevated triglyceride levels (TG $\geq$ 150 mg/dl to about 500 mg/dl)

Patents: 9,623,001, 9,693,986

U-2699: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a cardiovascular event (coronary revascularization, unstable angina, stroke and/or myocardial infarction) in an adult patient with elevated triglyceride levels

Patents: 9,918,954

U-2700: Use of Vascepa to reduce triglycerides in an adult patient with elevated triglyceride (TG) levels (about 200 mg/dl to less than about 500 mg/dl) and on rosuvastatin therapy

Patents: 10,265,287

U-2701: Use of Vascepa as an adjunct to statin therapy to reduce the risk of coronary revascularization and/or unstable angina in an adult patient with elevated triglyceride levels (TG $\geq$ 150 mg/dl to about 500 mg/dl)

Patents: 10,278,935

U-2702: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a cardiovascular event (cardiovascular death, coronary revascularization and/or unstable angina) in an adult patient with elevated triglyceride levels

Patents: 10,278,936

U-2703: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a CV event (CV death, coronary revascularization, unstable angina, stroke and/or myocardial infarction) in an adult patient with elevated triglyceride levels and diabetes mellitus

Patents: 10,278,937

U-2704: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a cardiovascular event in an adult patient with elevated triglyceride levels and at least one risk factor for cardiovascular disease

Patents: 10,383,840

U-2706: Use of Vascepa as an adjunct to statin therapy to reduce the risk of onset and/or recurrence of cardiovascular events in a patient who has escaped the unstable period after cardiovascular angioplasty

Patents: 9,198,892

U-2707: Use of Vascepa as an adjunct to statin therapy to reduce the occurrence of a cardiovascular event in an adult patient with hypercholesterolemia

Patents: 9,700,537

U-2743: Use of Vascepa as an adjunct to statin therapy to reduce the risk of unstable angina in an adult patient with established cardiovascular disease

Patents: 10,555,924

U-2744: Use of Vascepa as an adjunct to statin therapy to reduce the risk of stroke in an adult patient with established cardiovascular disease

Patents: 10,555,925

U-2756: Use of Vascepa as an adjunct to statin therapy to reduce the risk of cardiovascular death in an adult patient with established cardiovascular disease

Patents: 10,568,861

U-2762: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a major cardiovascular event in an adult patient with diabetes mellitus and two or more additional risk factors for cardiovascular disease

Patents: 10,576,054

U-2841: Use of Vascepa with high intensity statin therapy to reduce the risk of a CV event in an adult patient with elevated triglyceride levels and (1) established CV disease, or (2) diabetes mellitus and two or more additional risk factors for CV disease

Patents: 10,668,042

U-2959: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a third and further cardiovascular event in an adult patient with elevated TG levels ($\geq$150 mg/dl) and established cardiovascular disease

Patents: 10,786,478

U-2960: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a second or further cardiovascular (CV) event in an adult patient with elevated TG levels ($\geq$ 150 mg/dl) and diabetes mellitus and 2 or more additional risk factors for CV disease

Patents: 10,786,478

U-2961: Use of Vascepa as an adjunct to statin therapy to reduce the risk of myocardial infarction, stroke, both in an adult patient with type 2 diabetes mellitus

Patents: 10,792,267

U-2962: Use of Vascepa as an adjunct to statin therapy to reduce the risk of coronary revascularization in an adult patient with established cardiovascular disease

Patents: 10,792,270

U-2997: Use of Vascepa as an adjunct to statin therapy to reduce the risk of stroke in an adult patient with elevated triglycerides and atrial fibrillation

Patents: 10,842,766

U-3052: Use of Vascepa to reduce triglyceride levels in an adult patient on statin therapy and having atrial fibrillation and triglyceride levels of greater than 500 mg/dl

Patents: 10,881,632

U-3053: Use of Vascepa as an adjunct to statin therapy to reduce the risk of myocardial infarction in an adult patient with elevated triglyceride levels and established CV disease or diabetes mellitus and two or more additional risk factors for CV disease

Patents: 10,894,028

U-3126: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a second and further cardiovascular event in an adult patient with established cardiovascular disease

Patents: 11,000,499

U-3209: Use of Vascepa as an adjunct to statin therapy to reduce the risk myocardial infarction in an adult patient having atrial fibrillation or atrial flutter and elevated triglyceride levels

Patents: 11,103,477

U-3221: Use of Vascepa as an adjunct to statin therapy to reduce the risk of a cardiovascular event in a patient with prior percutaneous coronary intervention

Patents: 11,116,742

U-3240: Use of Vascepa to reduce triglyceride levels in an adult patient having triglyceride levels of at least about 500 mg/dl, on anticoagulant/antiplatelet/thrombolytic therapy, and having atrial fibrillation and/or atrial flutter

Patents: 11,154,526

U-3292: Use of Vascepa to reduce triglyceride levels in an adult patient on statin therapy and having atrial fibrillation or atrial flutter and triglyceride levels of about 500 mg/dl to about 2,000 mg/dl

Patents: 11,213,504

U-3358: Use of Vascepa to reduce the incidence of MI in an adult patient on statin therapy and with elevated triglyceride levels (>150 mg/dl), wherein the patient experiences atrial fibrillation and/or flutter instead of an incidence of MI

Patents: 11,298,333