Why Method of Treatment Patents for Repurposed Drugs Are Worth the Investment

By John E. Conour, Ph.D. and Daniel Gonzalez

Scientists, clinicians, and other investigators are discovering new uses for drugs previously known for different medical indications. Such "*drug repurposing*" (also called drug repositioning, profiling, or re-tasking) has great potential for providing clinicians with new therapeutic tools to combat diseases for which there are limited or no treatments available.[1]

Despite these implications, commercialization of repurposed drugs has little chance for success without patent protection that can attract funding and promise a reasonable return on investment. Investors such as angels, venture capitalists, and others (*e.g.*, research institutions, interest groups, etc.) are reluctant to pour capital into companies focused on repurposing drugs that are known chemical compounds for two main reasons. First, repurposed drugs are typically only patentable using method of treatment (MOT) claims (*e.g.*, "a method of treating disease X, comprising administering a therapeutically effective amount of drug Y") rather than composition of matter claims (*e.g.*, "a composition, comprising drug Y") because, although the MOT is presumably new, the repurposed drugs themselves are not. Second, MOT patents are less valued because they can potentially be more difficult to police for infringement (when it occurs, and who is the culprit), and infringement can be harder to prove. Yet, contrary to the conventional wisdom that MOT patents are second-tier to composition patents, companies are repurposing drugs, protecting them with MOT patents, and realizing significant successes for their efforts.

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[1] Sudeep Pushpakom *et al*., *Drug repurposing: progress, challenges and recommendations*, 18 NATURE REV. 41 (2019) (citing T.T. Ashburn *et al*., *Drug repositioning: identifying and developing new uses for existing drugs*, 3 NOT. REV. DRUG DISCOV. 675 (2004)).

Some of the world's most successful drugs were actually discovered through repurposing efforts and are or were at least originally protected only by MOT patents. For example, minoxidil (marketed as Rogaine®[2]) was first developed as a vasodilator, but it was repurposed to treat hair loss and generated over $700 million in sales for Upjohn by patent expiry in 1996[3]. Similarly, sildenafil (marketed as Viagra®[4]) was originally developed to treat angina, but it was repurposed to treat erectile dysfunction. Viagra reached global sales over $2.05 billion in 2013.[5] Atomoxetine[6] (marketed as Strattera®) was originally indicated as a therapeutic for Parkinson's disease, but it was repurposed to treat attention deficit hyperactivity disorder (ADHD), with sales reaching upwards of $855 million in 2016.[7] Similarly, rituximab was primarily intended to treat different types of cancers, but it was repurposed to treat rheumatoid arthritis (marketed as Retuxan®[8]) with sales topping $7 billion in 2014.[9] A more recent example is dextromethorphan (marketed as Nuedexta®) by Avanir Pharmaceuticals for the treatment of pseudobulbar affect.[10] Dextromethorphan is one of the two active ingredients in Nuedexta, and also happens to be one of the primary ingredients of the age old cough-suppressant Robitussin®. Nuedexta is protected

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[2] U.S. Pat. No. 4,596,812 (Claim 1 "A method of treating humans for alopecia which comprises topically applying to the human scalp an effective amount of a solution containing 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine and a solvent.").

[3] Norman M. Goldfarb, *When Patents Became Interesting in Clinical Research*, Journal of Clinical Research Best Practices 2(3): 2006.

[4] U.S. Pat. No. 6,469,012 (Claim 1 "A method of treating erectile dysfunction in a male animal, comprising administering to a male animal in need of such treatment an effective amount of a compound of formula (I): …").

[5] Sudeep Pushpakom *et al*., *supra* note 1 at 43 (citing D.J. Phillips, *Pfizer's Expiring Viagra Patent Adversely Affects Other Drugmakers Too.*, Forbes (Dec. 20, 2013, 12:06 PM), https://www.forbes.com/sites/investor/2013/12/20/pfizers-expiring-viagra-patent-adversely-affects-other-drugmakers-too/#33f0118168d4).

[6] U.S. Pat. No. 5,658,590 (Claim 1 "A method of treating attention-deficit/hyperactivity disorder comprising administering to a patient in need of such treatment an effective amount of tomoxetine.").

[7] Sudeep Pushpakom *et al*., *supra* note 1 at 43.

[8] U.S. Pat. No. 7,820,161 (Claim 1 "A method of treating rheumatoid arthritis in a human comprising (a) administering to the human more than one intravenous dose of a therapeutically effective amount of rituximab; and (b) administering to the human methotrexate." Upheld on IPR, *See* Celltrion, Inc. v. Biogen, Inc., No. IPR2016-01614 (P.T.A.B. Feb. 21, 2018)); *See also* U.S. Pat. No. 7,9,76,838 (Claim 1 "A method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient an antibody that binds to CD20, wherein the antibody is administered as two intravenous doses of 1000 mg.").

[9] Sudeep Pushpakom *et al*., *supra* note 1, at 43 (citing U. Starz, *Rituximab: how approval history is reflected by a corresponding patent filing strategy.*, 6 MABS 820 (2014).

[10] NEUDEXTA, https://www.nuedextahcp.com/ (last visited July 23, 2020) (pseudobulbar affect "(PBA) occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying.").

by three MOT patents[11] and has brought in hundreds of millions of dollars leading "Otsuka Holdings of Japan to purchase Avanir in 2014 for $3.5 billion."[12]

Hoping to follow in the footsteps of these giants, new companies like Biovista, Recursion Pharmaceuticals (Recursion), Roivant Sciences (Roivant), and others are focused on repurposing known drugs as a business model. For example, Biovista applies a "systematic discovery Artificial Intelligence platform to develop [a] pipeline of repositioned drug candidates in disease areas such as neurodegenerative diseases, epilepsy, oncology and orphan diseases."[13] Biovista currently boasts their own patent portfolio which includes multiple patents and applications whose first and broadest claim is a novel method of treatment.[14] Similarly, Recursion is successfully using machine-learning drug discovery to predict the safety of chemical entities.[15] As of 2019, Recursion "secured $121 million in new financing for its artificial intelligence programs."[16] Roivant is particularly interesting as it is a parent company that creates new subsidiaries around the drugs it aims to repurpose.[17] Although some of Roivant's subsidiaries are more successful than others[18], in 2017, the company raised over a billion

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[11] *See* U.S. Pat. No. 7,659,282 (Claim 1 "A method for treating pseudobulbar affect or emotional lability, the method comprising administering to a patient in need thereof dextromethorphan in combination with quinidine, wherein the amount of dextromethorphan administered comprises from about 20 mg/day to about 80 mg/day and wherein the amount of quinidine administered comprises from about 10 mg/day to less than about 30 mg/day with the proviso that the weight to weight ratio of dextromethorphan to quinidine is 1:0.5 or less."; *See* U.S. Pat. No. 8,227,484 (Claim 1 "A method for treating pseudobulbar affect or emotional lability, the method comprising administering to a patient in need thereof dextromethorphan in combination with quinidine, wherein the amount of dextromethorphan administered comprises from about 20 mg/day to about 60 mg/day and wherein the amount of quinidine administered comprises from about 10 mg/day to about 30 mg/day with the proviso that the weight-to-weight ratio of dextromethorphan to quinidine is 1:0.75 or less of quinidine."; U.S. Pat. RE38115 (A method of increasing the effectiveness of dextromethorphan in treating chronic or intractable pain, comprising administering to a patient suffering from chronic or intractable pain a therapeutically effective dosage of dextromethorphan or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective dosage of a debrisoquin hydroxylase inhibitor.").

[12] Julie Appleby, *How a Drug to Treat Crying Sent Sales Soaring*, N.Y. TIMES (May 12, 2017), https://www.nytimes.com/2017/05/12/business/media/pseudobulbar-affect-drug-advertising-sales.html.

[13] BIOVISTA, https://www.biovista.com/about/ (last visited June 29, 2020).

[14] *See* U.S. Patent No. 9,795,601 col. 29; U.S. Patent No. 10,172,854 col. 49; WO 2010/056710; WO 2010/068867.

[15] Conor Hale, *AI drug prospector Recursion Pharma nets $121M for its clinical programs*, FIERCE BIOTECH (July 15, 2019, 10:54 AM), https://www.fiercebiotech.com/medtech/ai-drug-prospector-recursion-pharma-nets-121m-for-its-clinical-programs.

[16] *Id.*

[17] Connie Loizos, *Roivant, which creates companies around abandoned drugs, just raised $1.1 billion from SoftBank*, TECHCRUNCH (Aug. 9, 2017, 6:32 AM), https://techcrunch.com/2017/08/09/roivant-which-creates-companies-around-orphaned-drugs-just-raised-1-1-billion-from-softbank/.

dollars in funding from SoftBank.[19] Clearly, there is a multifaceted market for repurposed drugs protected by MOT patents. So why are these companies successful when their IP is based on seemingly problematic MOT patents?

To answer this question, first consider the following limitations for MOT patents: (1) they have a more limited claim scope than composition patents; (2) they can be more difficult to enforce in an infringement action; and (3) a patent is not a right to practice, but only a right to exclude, as such, an enforceable composition patent on the repurposed drug itself can block the new MOT patent holder from practicing the method. Each of these issues is discussed below.

First, a MOT patent does not have the same scope as a composition patent on the same compound.[20] As scholars explain:

> [Product claims covering the compound] have always been the premium form of patent protection in the chemical industry. … A claim to the compound, per se, dominates every method of making that compound and every single use of that compound, every single mixture of different components that includes that compound, and every end use composition inclusive of the compound.[21]

Despite this, the more limited claim scope for a MOT patent is not necessarily problematic. New methods of treatment with a repurposed drug for a particular disease create exclusive and new markets for the repurposed drug. The fact that others may be using the same chemical compound for different reasons is not particularly relevant, because those uses would not be competing for the repurposed drug company's exclusive market share protected by the MOT patent. The primary use of the compound that matters is for the new treatment of a disease, and a MOT patent protects precisely that.

Second, unlike a patent on an apparatus or a compound, method claims consist of one or more steps to be performed. To impose liability for direct patent infringement[22], a plaintiff must prove that the defendant(s) performed every step articulated in the claim.[23] Thus, depending upon how a MOT claim is written, a patient could be performing one or more steps necessary to constitute an act of direct infringement (*e.g.*, obtaining a drug X and/or administering the drug X).

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[18] *See generally* Jianan Haung*, Can Drug Repositioning Work as a Systematical Business Model?*, 11 ACS CHEM. LETT. 1074 (2020), https://pubs.acs.org/doi/pdf/10.1021/acsmedchemlett.0c00122 (Axovant Gene Therapies (a subsidiary of Roivant) started as a drug repurposing company, but then transferred to R&D cooperation after a series of failures in clinical trials).

[19] Loizos, *supra* note 15.

[20] Sean B. Seymore, *Patenting New Uses for Old Inventions*, 73 VAND. L. REV. 479, 498 (2020).

[21] *Id* (quoting HAROLD C. WEGNER, PATENT LAW IN BIOTECHNOLOGY, CHEMICALS, AND PHARMACEUTICALS 177 (1992)).

[22] 35 U.S.C. § 271(a) (2012).

[23] *Akamai Technologies, Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (per curiam) ("Direct infringement under § 271(a) occurs where all steps of a claimed method are performed by or attributable to a single entity.").

However, suing patients for patent infringement is commercially untenable.[24] Despite this limitation, there are options for MOT patent enforcement.

One option is the possibility of suing the prescribing physician, the pharmacist who provided the repurposed drug in the appropriate dosage, or some other actor under a divided infringement theory[25] and/or under an induced infringement theory.[26] Although Congress, under 35 U.S.C § 287(c), carved out certain immunity for physicians from patent infringement while performing "medical activities," "[the] defense does not cover the practice of a patented use of a composition of matter …."[27] So, it is possible to enforce a MOT patent against a physician as an induced infringer; but again, it may not make good business sense to do so, unless there is a large number of infringing physicians, which could suggest a central actor. An ideal target for enforcing a MOT patent would be a rival pharmaceutical company. However, if that rival has not included the new indication on their label, it is challenging to hold the rival liable for infringement as they have neither directly infringed the patent nor have they guided others to do the same. There are ways around this though. If a patentee can claim a new combination of known drugs, or a specific dosing regimen or dosage form for a single repurposed drug that is necessary for the new method of treatment, these approaches would limit the ability of physicians to prescribe the repurposed drug product for an off-label use.[28] Moreover, should a rival pharmaceutical company begin providing a dosage form necessary for the new method of treatment, they could be liable for infringement. Of course, while these approaches can help address the off-label use issue, they may complicate the approval process because the FDA will need to be convinced that the new combination and/or dosing regimen/dosage form are safe and effective. As a

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[24] *See* Seymore, *supra* note 20, at 506.

[25] Divided infringement is a type of direct infringement under 35 U.S.C. § 271(a) but according to the Federal Circuit:

> "We will hold an entity responsible for others' performance of method steps in two sets of circumstances: (1) where that entity directs or controls others' performance, and (2) where the actors form a joint enterprise. To determine if a single entity directs or controls the acts of another, we continue to consider general principles of vicarious liability. In the past, we have held that an actor is liable for infringement under § 271(a) if it acts through an agent (applying traditional agency principles) or contracts with another to perform one or more steps of a claimed method." *Limelight Networks, Inc.*, 797 F.3d at 1022-23.

[26] *See Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766 (2011) ("induced infringement under § 271(b) requires knowledge that the induced acts constitute patent infringement."). Induced infringement is a type of indirect infringement under 35 U.S.C. § 271(b) where a defendant must be aware that they are guiding or directing the user to an infringing act. There must be an underlying act of direct infringement under § 271(a) for the plaintiff to establish liability on a defendant under § 271(b).

[27] Timothy R. Holbrook, *Method Patent Exceptionalism*, 102 IOWA L. REV. 1001, 1021 (2017) ("'[Section 287(c)] defines "medical activity" as 'the performance of a medical or surgical procedure on a body" but excludes from this defense three types of activity: the use of a patented machine, manufacture, or composition of matter; practice of a patented use of a composition of matter; and practice of a process of a biotechnology patent.'" Citing 35 § U.S.C. 287(c)(2)(A)).

[28] Sudeep Pushpakom et al., *supra* note 1 at 51 ("However, off-label use can be limited if the new repurposed indication requires a unique formulation and/or a dosage regimen that cannot easily be achieved with the available generic versions of the drug.").

result, efficiencies from starting with known compounds and building off well-established safety data start to become less relevant the more one changes the known formulation.[29] Despite these complexities in enforcement, MOT patents still effectively deter the most important would-be infringers (rival pharmaceutical companies), as discussed below.

Third, a patent on the repurposed drug itself can block the MOT patent holder from practicing the claimed method. However, even though a patent holder of the underlying composition of matter can prevent a patentee from practicing a method of treatment that uses the composition, this battle of the patents is a two-way street. Just as much as the composition patent holder can exclude the MOT patent holder from practicing their invention, the MOT patent holder can exclude the composition patent holder from using their compound for the new indication.

MOT patents are not necessarily as limited as one might think. Rather, MOT patents also provide their own advantages such as strategically carving out exclusive markets for the repurposed drug, providing tactical leverage in licensing, and potentially extending market exclusivity to keep competitors at bay. In addition, a new MOT patent can become more valuable the closer the underlying composition patent is to expiring. Holders of aging composition patents may be more willing to cross-license, or simply acquire the rights for a new MOT patent that can provide a new market for their drug or extend the period of exclusivity. On the other hand, there may also be opportunities for innovators who held the original composition patents to profit by supplying the API for the repurposed drug, and in effect, forming a partnership with the company repurposing the drug.

Moreover, if the "repurposed" indication has the potential for generating significant profit, the patentee of the MOT patent can have a great deal of leverage over the composition patent holder to force favorable licensing terms. For example, consider Gilead®'s investigational antiviral drug, remdesivir. As of yet, remdesivir is the only known drug demonstrated to reduce the hospitalization time of patients diagnosed with COVID-19.[30] On January 21, 2020, a Chinese patent application was filed claiming the use of remdesivir "for the treatment of 2019 novel coronavirus (2019-nCoV) caused disease or infection ...."[31] Whether or not the Chinese patent application will ultimately issue as a valid patent remains to be seen, but the fact remains that the Chinese application represents a potential source of leverage for ideal cross-licensing terms with Gilead.

Further, MOT patents are effective barriers to entry of competitors and routinely held valid. One of many examples[32] demonstrating their value is the litigation surrounding the drug atomoxetine.

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[29] N. Nosengo, *New tricks for old drugs*, 534 NATURE 314, 316 (2016) ("the standard business case for repositioning– that costs are slashed because safety tests are already in the bag– works only if the dose and mode of administration remain similar.").

[30] J.H. Beigel et al*., Remdesivir for the Treatment of Covid-19 --Preliminary Report*, NEW. ENG. J. MED., May, 22, 2020, at 1 (Remdesivir was superior to placebo in shortening the time to recovery [(11 days as compared with 15 days)] in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection.").

[31] CN111265532A, Application of substituted aminopropionate compound in treatment of 2019-nCoV infection, Claim 1.

[32] *See also Pfizer Inc., v. Teva, USA Inc*., 803 F.Supp.2d 409, 458-59 (E.D. Va. 2011) (Regarding the method of treatment patent for Viagra: "[T]he court FINDS that Teva's proposed generic equivalent of Viagra would INFRINGE the ′012 patent and FINDS the ′012 patent is VALID and ENFORCEABLE.

In *Eli Lilly & Co. v. Actavis LLC*, the Federal Circuit was presented with an ANDA case involving a MOT patent between Lilly and seven generic manufacturers who had invalidated Lilly's patent in the District Court for the District of New Jersey.[33] The Federal Circuit reversed the District Court, conclusively stating that the MOT patent was valid, and the defendants were liable for both contributory and induced infringement.[34] The claim at issue was claim 1, which read "[a] method of treating attention-deficit/hyperactivity disorder comprising administering to a patient in need of such treatment an effective amount of tomoxetine."[35] The District Court '"sustained the '590 patent against the defendants' challenges on the grounds of inequitable conduct, anticipation, obviousness, and non-enablement . . . [but] held the claim invalid for lack of utility because 'experimental data showing the results of treatment of ADHD were not included in the specification.'"[36] At the time of filing, the applicant did not submit experimental data to support the use of tomoxetine for ADHD, but prior to the patent issuing, such data were submitted. The Federal Circuit clarified that experimental data are not necessarily needed to prove utility. Instead, the question is whether the information presented in the specification would cause "one skilled in the art to question the objective truth of the statement of utility or its scope," and if so, the onus shifts to the applicant to provide additional support.[37] However, the examiner did not doubt the applicant's assertion that atomoxetine could be useful as a treatment for ADHD. Additionally, the relationship between atomoxetine and other neurotransmitters like norepinephrine was established enough in the specification that the assertions of utility were not "contrary to generally accepted scientific principles."[38]

Therefore, the Clerk is DIRECTED to enter judgment for Pfizer on the Amended Complaint and Amended Counterclaim in this case, in accordance with this Opinion and Final Order."); *See also Avanir Pharmaceuticals, Inc., v. Actavis LLC.*, 36 F.Supp.3d 475, 510 (D. Del. 2014) (Regarding the method of treatment patents for Nuedexa: "The parties shall meet and confer and submit, no later than May 5, 2014, a proposed order consistent with the Memorandum Opinion, to enter final judgment: (i) FOR Plaintiffs and AGAINST Defendants for infringement of the '282 and '484 patents, including any appropriate remedy, (ii) AGANST Plaintiffs and FOR Defendants for infringement of the '115 patent, and (iii) FOR Plaintiffs and AGAINST Defendants for validity of the '282, '484, and '115 patents.").

[33] *Eli Lilly & Co. v. Actavis LLC*, 435 F.App'x 917 (Fed. Cir. 2011).

[34] *Id.* at 919 (Fed. Cir. 2011) ("The [District] [C]ourt also held that if the claims were valid the defendants would be liable for inducement to infringe, but that they would not be liable for contributory infringement. The ruling of invalidity for lack of utility, and the ruling that contributory infringement does not also apply, are reversed. The district court's other rulings are affirmed.").

[35] *Id* at 919.

[36] *Id* at 923.

[37] *Id* at 924-95 (quoting *In re Langer,* 503 F.2d 1380, 1391 (C.C.P.A 1974) ("[A] specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope.") and quoting *In re Brana,* 51 F.3d 1566 (Fed. Cir. 1995) ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

[38] *Eli Lilly & Co. v. Actavis LLC*, *supra* note 33 at 926 (citing *In re Marzocchi*, 58 C.C.P.A. 1069, F.2d 220, 223 (C.C.P.A. 1971).

The *Lilly* case teaches entrepreneurs and investors considering repurposing drugs two critical lessons. First, and most importantly, that MOT patents can be enforced as an effective weapon against infringers. And second, that advanced clinical research data are not necessary to obtain a valid MOT patent, so long as the specification discloses assertions of utility not contrary to generally accepted scientific principles, and the claims are otherwise valid as novel, non-obvious, and enabled. The second point is key for startup companies that are seeking MOT patent protection prior to pitching their repurposed drug to investors. For these reasons, MOT patents are legally defensible and can effectively protect repurposed drugs.

In summary, MOT patents have a proven history of providing a commercially viable foundation for entrepreneurs to build companies or sell/license the intellectual property rights surrounding their repurposed drugs. Despite their perceived shortcomings, MOT patents cover and protect exactly what makes them profitable– the market created by the new use of the known drug. MOT patents are enforceable against key competitors and can be used to effectively block would be infringers. Investors would be wise to invest in repurposed drugs protected by MOT patents. The benefits of establishing exclusive markets, tactical leverage in licensing, and the ability to extend market exclusivity make pursing MOT patents worth the investment.

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