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Repurposing - Finding New Uses for Old (and Patented) Drugs: Bridging the "Valley of Death," to Translate Academic Research Into New Medicines

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**Repurposing – Finding New Uses for Old (and Patented)
Drugs: Bridging the “Valley of Death,” to Translate
Academic Research into New Medicines**

I. INTRODUCTION	143
II. DRUG REPURPOSING.....	144
A. Growth of Drug Repurposing	144
B. Academic Drug Development and the “Valley of Death” ...	146
C. Repurposing to Traverse the Valley of Death—Is There Sufficient Exclusivity?.....	148
D. Repurposing to Traverse the Valley of Death—Can I Find New Uses for <u>Your</u> Drug?	150
III. PATENT LAW AND REPURPOSING.....	151
A. Statutory Law and History	151
B. Statutory Interpretation and Common Law.....	153
1. Creation of 35 U.S.C. § 271(e)(1)	153
2. Eli Lilly v. Medtronic: Setting the Stage for Merck v. Integra	154
3. Merck v. Integra	154
a. The facts in Merck v. Integra	155
b. The issue of safe harbor protection scope.....	156
c. Scope includes research directed to IND and NDA filing	156
d. The scope of the safe harbor protection extends beyond safety studies	157
e. Scope not limited to studies included in IND, NDA or ANDA filings	157
4. After Merck v. Integra	158
C. Summary of Current Law the Legal Issue.....	160
IV. APPLYING THE LAW TO DRUG REPURPOSING.....	160
A. Repurposing Research.....	160
B. Implications of Merck and Momenta (M&M) for Repurposing Research.....	161
C. Public Policy Considerations for Repurposing Research.....	163
1. Society Needs New Medicines – Repurposing Serves the Greater Social Good.....	163
2. From Fairies to Financial Bias.....	164
3. Innovation – To Advance Science and the Useful Arts –	

Such as Medicine	165
V. CONCLUSION	166

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I. INTRODUCTION

Most people have experienced the pain of seeing loved ones suffer, and perhaps die, from diseases that no adequate treatments exist for. We all understand, in very personal ways, the need for new and better therapies. However, the pipeline of new medicines from the pharmaceutical industry has been dwindling as research and development costs increase, and as productivity has been declining.¹ As a society, we now face a serious problem—indeed, a tipping point. While the pharmaceutical industry was once viewed as a growth industry embodying the spirit of innovation, its pipeline of new medicines is drying up. Could it be that the pharmaceutical industry, at least in its current form—focused on “blockbuster drugs”—has made that fateful transition from a growth—i.e. innovation-driven—industry, to a mature industry? If that is the case, where will the new medicines come from, especially for currently untreated diseases—the “unmet medical needs”? This comment will present legal and public policy arguments in support of one solution to this problem: drug repurposing; in particular, drug repurposing that is performed in university research labs and directed towards unmet medical needs. This comment will also include a fairly detailed description of the drug development process and analysis of the pharmaceutical industry. This is in part a bias of the author, who has previously worked in the pharmaceutical and biotechnology industries in drug development and co-founded two biotechnology companies, one of which is focused on drug repurposing.

Drug repurposing, sometimes referred to as repositioning, is increasingly being pursued as a solution to the problem of dwindling pharmaceutical pipelines; it is being proposed in both industrial and academic drug development settings.² Repositioning is the process whereby a drug that is patented for treating a particular disease is discovered to be useful for treatment of a second disease, and then is developed further for that purpose.³ But can a researcher explore new uses for a patented drug without infringing on the patent owner’s patent under 35 U.S.C. § 271? The answer to this question is a qualified “yes.”

1. Ish Khanna, *Drug Discovery in Pharmaceutical Industry: Productivity Challenges and Trends*, DRUG DISCOVERY TODAY at 1088, 1088 (2012).

2. EL Tobinick, *The Value of Drug Repositioning in the Current Pharmaceutical Market*, 22 DRUG NEWS & PERSP. 119, 119 (2009); Francis S. Collins, Comment, *Mining for Therapeutic Gold*, 10 NATURE REV. DRUG DISCOVERY 397 (2011); Ted Agres, *New Life for Old Drugs*, DRUG DISCOVERY & DEV. (July 29, 2011), www.dddmag.com/articles/2011/07/new-life-old-drugs; Ann Thayer, *Drug Repurposing*, CHEMICAL AND ENGINEERING NEWS, Oct. 1, 2012.

3. *Rescuing and Repurposing Drugs*, NATIONAL INSTITUTES OF HEALTH, [http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html%20\(last visited March 19, 2013\)](http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html%20(last%20visited%20March%2019%202013)).

This comment will present background as to why drug repositioning, and especially repurposing, has moved to the forefront of public—e.g. university, government-funded research—and private drug development efforts. Then, the various intellectual property and business issues surrounding repurposing will be presented. Case law will be reviewed to address the key legal question: *to what extent can a person or company perform research directed towards repurposing another company's patented drug*, under the protective umbrella of the safe harbor protection provided by 35 U.S.C. § 271(e)(1)? To help answer the question, this comment will review the judicially created guiding principles that establish when repurposing research is permitted safe harbor protection.

Since the courts have concluded that the 35 U.S.C. § 271(e)(1) safe harbor protections apply to an expanding array of repurposing research activities, this comment will conclude with a look forward at this continuing trend. An argument is made that the expanding protections afforded repurposing research is good public policy when balanced against the fact that pharmaceutical companies are not adequately pursuing certain unmet medical needs of society. It is argued that allowing repurposing research serves the broader interests of society by advancing science and the useful arts, such as medical practice. Lastly, the expanding scope of the safe harbor protection of repurposing research should continue because university researchers and small companies will pursue diseases that larger pharmaceutical companies will not explore with their patented drugs, such as diseases that afflict smaller populations of people or those with limited financial resources.

II. DRUG REPURPOSING

Drug repositioning is the process of finding a new use for an existing drug. The repositioning process is sub-categorized as: (a) *Repurposing*, if the first drug is already approved for clinical use in humans after achieving New Drug Application (NDA) approval, and (b) *Rescuing*, if the first drug did not yet achieve NDA approval, so is not in commercial use.⁴ The more common situation, and the focus of this comment, is drug repurposing.

A. Growth of Drug Repurposing

Despite consistently increasing spending on drug development in the U.S., the number of new drugs—or New Chemical Entities (NCEs)—produced by the pharmaceutical industry (pharma) has been decreasing for the last twenty years.⁵ Initially, this decrease led to a series of mergers and acquisitions

4. *Id.*

5. Khanna, *supra* note 1, at 1089.

(M&A's), as companies attempted to populate their drug development pipelines by acquiring innovation from other companies. Notable examples have been GlaxoWellcome and SmithKline Beecham in 2000, and multiple M&A's in 2009, including Pfizer/Wyeth and Merck/Schering-Plough.⁶ Eventually, this lack of innovation leading to NCEs had an even more profound impact on the industry as blockbuster drugs⁷ began to come off patent, in what has been referred to as the "patent cliff."⁸ As market exclusivity was lost and generic drugs replaced patented drugs, revenue dropped and the industry experienced the most dramatic downsizing in its history.⁹

As the pharmaceutical industry emerges from this massive downsizing and restructuring, it is struggling both to redefine itself, as well as to find future sources of new medicines for patients. One strategy that pharma is embracing is an increasing trend of in-licensing potential NCEs from biotechnology companies or universities.¹⁰ Meanwhile, the public sector is stepping in to fill this gap in pharmaceutical innovation. Recognizing the public health implications of this dearth of innovation in pharma, President Obama provided funding in 2012 to launch the National Center for Advancing Translational Sciences (NCATS) within the National Institutes of Health (NIH).¹¹ NIH Director Francis Collins stated that:

This action marks a major milestone in efforts to revolutionize the science of translation. NCATS provides our nation with an opportunity to forge a new paradigm for translational research that involves government, academia, industry, philanthropy, and patient advocacy

6. Tracy Staton, *Pharma M&A: 10 Years, 1,345 Deals, \$695B*, FIERCEPHARMA (March 26, 2010), <http://www.fiercepharma.com/story/pharma-m-10-years-1-345-deals-694b/2010-03-26>.

7. Pierre Jacquet, Elizabeth Schwarzbach, & Ilan Oren, *The New Face of Blockbuster Drugs*, 29 IN VIVO: THE BUS. & MED. REP. 2, 2 (2011) (defining a blockbuster drug as one that generates more than \$1 billion in revenue per year).

8. Charlotte Harrison, *The Patent Cliff Steepens*, 10 NATURE REVIEWS DRUG DISCOVERY 12, 12 (2011); Joseph Jimenez, *The CEO of Novartis on Growing After a Patent Cliff*, HARV. BUS. REV. (Dec. 2012) at 39.

9. John D. Carroll, *Top 10 Pharma Layoffs of 2012*, FIERCEBIOTECH (Oct. 18, 2012) <http://www.fiercebiotech.com/special-reports/top-10-pharma-layoffs-2012>; Duff Wilson, *Drug Firms Face Billions in Losses in '11 as Patents End*, N.Y. TIMES (Mar. 6, 2011), http://www.nytimes.com/2011/03/07/business/07drug.html?pagewanted=all&_r=1&.

10. Heather Cartwright, *A Review of Deal Making in 2011*, 1 PHARMADEALS REVIEW 15, 15 (2012); Sergio Garcia, *Emerging Trends in Biotech/Pharmaceutical Collaborations*, THE LICENSING J. 1, 1 (2008), http://www.mavery.com/academic/Garcia_Avery_Emerging_Trends.pdf.

11. The NIH is the primary public source of funding for biomedical research in the United States, investing over \$30.9 billion each year. Funding is primarily through grants, which were made to over 300,000 researchers in 2,500 medical schools, universities, and research institutions. *NIH Budget: Research for the People*, NATIONAL INSTITUTES OF HEALTH, <http://www.nih.gov/about/budget.htm> (last visited Mar. 21, 2013).

groups . . . I believe we can work together to achieve our common goal: speeding the movement of scientific discoveries from the lab to patients.¹²

B. Academic Drug Development and the “Valley of Death”

Pharma experts, including former Chairman and CEO of Merck, Roy Vagelos, argue that the public sector—universities and the NIH—have little experience in drug development and should leave drug development work to the pharmaceutical industry. In testimony before the United States House of Representative’s Committee on Appropriations, Dr. Vagelos stated that the NIH and NCATS should focus on funding basic research and avoid getting involved in drug repurposing:

[T]rying to find a use for a drug that has not been approved is a fishing expedition that has a very low probability of success. As for repurposing of drugs, I would recommend that the NIH not support clinical studies of marketed drugs. Such studies that are aimed at obtaining additional claims for drugs already being sold should be funded by the company that owns the drug and will benefit financially from the additional claim.¹³

Is Dr. Vagelos correct? Should university researchers and the NIH stay out of drug repurposing research? While he has some valid points, a case can be made that his recommendation is both biased and wrong.

While academic (i.e. NIH-funded) researchers are adept at identifying new proteins that can be pursued as drug targets, and identifying initial drug lead molecules that bind to these proteins, they often lack the knowledge and expertise needed to go from these basic research discoveries through the various pre-clinical studies, to reach a drug lead molecule in human clinical trials. Indeed, of 5000, pre-clinical drug candidates, on average only five will make it into human clinical trials. Of these, only one will make it to NDA approval.¹⁴ This gap between basic research discovery and the molecule that makes it into the clinic has been called the “valley of death,” in part because

12. Francis S. Collins, *NIH Launches National Center for Advancing Translational Sciences*, NATIONAL INSTITUTES OF HEALTH (Dec. 23, 2011), http://www.nih.gov/about/director/ncats/12232011_statement_NCATS.htm.

13. *Budget Hearing of the Dep’t of Health and Human Services Before the H. Subcomm. Of Labor, Health, and Human Services Comm. on Appropriations*, 112th Cong. 4 (2012) (statement of P. Roy Vagelos, M.D., President of Merck & Co., Inc.), available at <http://appropriations.house.gov/calendar/eventsingle.aspx?EventID=281151>.

14. Sandra Kraljevic, Peter J. Stambrook & Kresimir Pavelic, *Accelerating Drug Discovery*, 5 EMBO REPORTS 837, 837 (2004).

there is a weeding out in going from 5000 to five drug candidates, in a process that is only traversed by those who have the appropriate skill set, which is typically those in industry.¹⁵ However, because repurposed drugs have already had pre-clinical studies performed on them for another disease indication, they serve to bridge the “valley of death,” making it possible to turn basic research discoveries into new medicines much more efficiently.¹⁶ Quite simply, it will be easier for academic labs to traverse the drug development “valley of death” if they are repurposing, because repurposing will not require as many pre-clinical studies, which are typically areas of expertise for only industrial scientists.

Yet, despite the promise that repurposing offers for rapidly translating research into therapeutics, there is strong skepticism by some industry leaders that NCATS, with its focus on repurposing, will achieve its goal. This skepticism is exemplified by Dr. Vagelos’ testimony before Congress, when he said: “[d]oes anyone in the audience believe that there is something that NCATS is going to do that the industry thinks is critical and that they are not doing? That is incredible to think that. If you believe that you believe in fairies.”¹⁷ These comments by this well-respected industry leader and former Merck CEO should be put into proper context. Dr. Vagelos represents the pharmaceutical industry; an industry in the midst of a historic structural change due to its lack of productivity.

Congress funded NCATS, and is moving forward with its mandate to bridge the valley of death via drug repurposing. NCATS was allocated \$575 million of the NIH’s \$30.6 billion budget to “tackle bottlenecks in drug development,” with emphasis on drug rescuing and repurposing.¹⁸ The NIH has even made available a collection of compounds for drug repurposing and repositioning studies, to be done in collaboration with the pharmaceutical companies that own the composition of matter intellectual property.¹⁹ As of June 2012, companies

15. Sharon Begley & Mary Carmichael, *Desperately Seeking Cures*, NEWSWEEK, May 31, 2010, <http://www.newsweek.com/id/238078/ouput/print>; David Bornstein, *Helping New Drugs Out of Research’s “Valley of Death,”* N.Y. TIMES (May 2, 2011, 9:15 PM), <http://opinionator.blogs.nytimes.com/2011/05/02/helping-new-drugs-out-of-academias-valley-of-death/>.

16. Asher Mullard, *An Audience With . . . Francis Collins*, 10 NATURE REVIEWS DRUG DISCOVERY 14, 14 (2011); Collins, *supra* note 2.

17. John LaMattina, *The NIH Is Going to Discover Drugs . . . Really?*, FORBES (May 15, 2012, 12:40 PM), <http://www.forbes.com/sites/johnlamattina/2012/05/15/the-nih-is-going-to-discover-drugs-really/>.

18. Collins, *supra* note 12; Jocelyn Kaiser, *Acting Director Thomas Insel Explains New NIH Translational Center’s Aims and Structure*, SCIENCE INSIDER (Jan. 10, 2012, 10:53 AM), <http://news.sciencemag.org/2012/01/acting-director-thomas-insel-explains-new-nih-translational-centers-aims-and-structure>.

19. *Library of Industry-Provided Agents*, NATIONAL INSTITUTES OF HEALTH, <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory.html>

providing compounds for repurposing through the NCATs initiative included: Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutical Research & Development, L.L.C., Sanofi, Pfizer, AstraZeneca, and Eli Lilly and Company.

C. Repurposing to Traverse the Valley of Death—Is There Sufficient Exclusivity?

The pharmaceutical industry is increasingly pursuing drug repurposing, with Thompson Reuters projecting \$20 billion in sales from repositioned drugs.²⁰ Given that the cost of developing a single drug is estimated to exceed \$1 billion,²¹ companies must obtain market exclusivity through patent protection to justify and potentially recoup this large investment. This concern is present even if drug development costs are somewhat lower, at least on the front end, as in the case of drug repurposing. A key issue that any company pursuing repurposing must face is whether market exclusivity can be obtained for their repurposed drugs. When a company is repurposing a drug that another company has a composition of matter (CoM) patent for, it cannot easily achieve market exclusivity via patent protection unless it licenses the CoM patent from the owner. Furthermore, the CoM patent protection associated with the original use will often have run out by the time the repurposing research, clinical trials, and regulatory approvals have been completed.

Once a new use is found for a drug, how can the company that has found this new use achieve market exclusivity when CoM patent protection is typically no longer available? Under the Orphan Drug Act of 1983,²² market exclusivity is offered for seven years in the United States, (Europe offers ten years), as long as the drug is for a “rare disease,” which in the United States means the disease afflicts less than 200,000 people.²³ The list of repurposed drugs being used to treat rare diseases include: Azathioprine, Bleomycin, Colchicine, Cyclosporine, Cycloserine, Eflornithine, Everolimus, Histrelin, Infliximab, Interferon alfa and Rituximab.²⁴ Pursuit of drugs to treat rare diseases is clearly in the public interest, and is also typically of more interest to

(last visited Mar. 22, 2013); *Five More Pharmaceutical Companies Join NIH Initiative to Speed Therapeutic Discovery*, NATIONAL INSTITUTES OF HEALTH (June 12, 2012, 10:00 AM), <http://www.nih.gov/news/health/jun2012/ncats-12.htm>.

20. Thayer, *supra* note 2, at 18.

21. *Drug Developers Are Aggressively Changing the Way They Do R&D*, TUFTS UNIVERSITY (Jan. 5, 2011), http://csdd.tufts.edu/news/complete_story/pr_outlook_2011.

22. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2051 (1983).

23. Kiran N. Meekings, Cory S.M. Williams, & John E. Arrowsmith, *Orphan Drug Development: An Economically Viable Strategy for Biopharma R&D*, DRUG DISCOVERY TODAY at 660, 660 (2012).

24. Thayer, *supra* note 2, at 18.

university research laboratories and small companies, as opposed to larger pharmaceutical companies that favor products targeting larger markets.

One can also obtain market exclusivity for repurposed drugs via Method of Use (MoU) patent protection. Examples of successfully marketed drugs in this category are Celgene's Thalomid^{®25} and the related drug Revlimid[®],²⁶ for Leprosy and multiple myeloma. However, since physicians can and do prescribe drugs off-label, such MoU protection is considered weak, because it limits pricing options. If the second drug is priced too high, physicians can simply prescribe the first drug for off-label use. One could then ask if the physician who prescribes off-label to avoid high prices is infringing, but prosecutions seem unlikely.

The problem of off-label use, limiting the value of MoU patents, applies only to repurposed drugs, not to rescued drugs. If a drug has made it through many of the human clinical trials required by the Food and Drug Administration (FDA), yet has never received NDA approval, and therefore is not on the market, off-label use is not possible. Thus, MoU patents can be more strongly considered for rescued drugs. Drug rescuing inherently provides a type of market exclusivity, and in that sense is preferable to drug repurposing from a business perspective.

A final option for achieving market exclusivity is to patent a new formulation or delivery route, such as patch versus oral delivery or dosage form, for a given drug molecule.²⁷ However, such changes must be more than just nonobvious. While the new drug formulation might be nonobvious to someone skilled in the art, that is not enough. Additionally, the new formulation must not be obvious to try, under the "obvious to try doctrine"²⁸ after *KSR Int'l v. Teleflex*.²⁹ This doctrine has raised the bar, making the reformulation route to market exclusivity more challenging. Perhaps the most powerful route to market exclusivity is to use the drug in combination with a second drug, where the two drugs act in a complementary, or even synergistic, manner. While such combination therapies might be protected via a MoU patent, if the combined effect of the two drugs is unanticipated, it is possible to obtain the much-preferred CoM protection,³⁰ a strategy being systematically employed at

25. Agres, *supra* note 2; U.S. Patent No. 8,204,763 B2 (filed Dec. 13, 2010).

26. U.S. Patent No. 7,968,569 B2 (filed May 15, 2003).

27. See U.S. Patent No. 7,230,012 B2 (filed June 30, 2003).

28. Anna C. Chau & Irving N. Feit, *The Obvious to Try Doctrine: Its Use, Misuse, and Abuse*, 91 J. PAT. & TRADEMARK OFF. SOC'Y 89, 93 (2009).

29. 550 U.S. 398 (2007).

30. U.S. Patent No. 7,915,265 B2 (filed Feb. 15, 2006); U.S. Patent No. 8,067,433 B2 (filed Nov. 8, 2006).

Zalicus.³¹ Examples of successful combination drugs include the antiviral cocktails—e.g. Trizivir, which is made up of abacivir, zidovudine, and lamivudine. Other combination drugs include Caduet, to treat both hypercholesterolemia (atorvastatin) and hypertension (amlodipine), as well as a combination of Advair and Seretide to treat asthma and chronic obstructive pulmonary disease (COPD).

D. Repurposing to Traverse the Valley of Death—Can I Find New Uses for Your Drug?

Is drug repurposing something that can only be pursued by the company that developed the original drug and use? This question is not without controversy; Dr. Vagelos, in his testimony to Congress on repurposing and NCATS, commented that “studies that are aimed at obtaining additional claims for drugs already being sold should be funded by the company that owns the drug and will benefit financially from the additional claim.”³² This argument seems valid if in fact the company will explore all potential alternative uses for its patented drugs, but as is discussed above, pharmaceutical companies have little incentive to pursue certain disease classes, such as rare and neglected diseases. It is perhaps due to comments like this that the NIH-funded repurposing initiative is being limited to partnerships with the companies that own the CoM patents on the compounds, and why the only compounds these companies have offered to the NIH have significant patent terms remaining—typically more than ten years.³³ Only in this way, and through yet-to-be negotiated licensing terms, can the companies providing these molecules to the NIH recoup the untapped value from their intellectual property assets.

Thus, pharma is apparently maintaining tight control over which drugs can be the subject of repurposing studies via the NCATS program. But, does pharma really have this much control over repurposing studies? Is it true that other companies or academic researchers cannot explore new uses for established and patented drugs on their own, for drugs with little or no patent term remaining, or for any drugs beyond the fifty-eight that companies have cherry-picked and offered to NCATS?³⁴ If the company owning the original CoM protection is not exploring, or is unaware of, these new potential therapeutic uses, how is the greater public good being served? While it is to be expected that a pharmaceutical company that owns the CoM patent for a drug

31. *cHTS Technology: Treating Disease Through Multiple Biological Pathways*, ZALICUS, <http://www.zalicus.com/discovery-technologies/chts-technology.asp> (last visited Mar. 19, 2013).

32. *Budget Hearing of the Dep't of Health and Human Services*, *supra* note 13.

33. *Library of Industry-Provided Agents*, *supra* note 19.

34. *Id.*

molecule might not be in favor of the empowerment of other companies or researchers to explore new uses for their patented drug—just as they do not favor the current empowerment of other companies to develop generic alternatives before their CoM patent protection expires—the question remains, are such repurposing studies legally permitted, and are they in the public interest? That is, do they serve the purpose outlined in the United States Constitution, Article I, Section 8, Clause 8, “To promote the Progress of Science and Useful Arts”?³⁵ This comment argues that such studies are in the public interest, are supported by a series of recent Supreme Court decisions, and do indeed promote the progress of science and the useful arts, specifically medical practice. Repurposing studies can be done, following the guidelines provided by the Court, without asking for permission from the pharma patent owner; this opens up the source of potential new molecular treatments to the thousands of molecules that pharma is sitting on, rather than just the handful that were offered to academic researchers via NCATS. Indeed, it is a rather clever strategy for the industry to offer a small number of molecules to researchers for a small price (license terms to be negotiated), when in reality these repurposing researchers may already have access to everything—but perhaps they do not know that is the case.

III. PATENT LAW AND REPURPOSING

What is the law that provides access to others’ patented molecules for repurposing studies and what are the limitations of that access under the safe harbor shield? This section will provide the legal foundation that defines the safe harbor protection of repurposing studies, based on the original statute, and various cases where that statute has been interpreted, most notably, *Merck v. Integra*.³⁶

A. Statutory Law and History

Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act”),³⁷ which led to the creation of 35 U.S.C. § 271(e)(1):

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented

35. U.S. CONST. art. I, § 8, cl. 8.

36. *Merck KGaA v. Integra Lifesciences. I, Ltd.*, 545 U.S. 193.

37. The Drug Price and Competition and Patent Term Restoration Act of 1984 is referred to, more informally, as the Hatch Waxman Act. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) . . .) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.³⁸

This statute was passed to address the needs of the generic drug industry, which complained that after a patent on a drug expired, the generic company still needed to do many years of research and clinical studies before they could enter the market with their generic version of the drug. This additional drug development period effectively gave the original CoM patent-holder a *de facto* extension beyond the twenty-year term, which the generic drug manufacturer argued was unjust. For this reason, Congress provided a safe harbor protection,³⁹ to allow generic companies to perform the clinical studies that the Food and Drug Administration (FDA) requires for an Abbreviated New Drug Application (ANDA).⁴⁰ An ANDA will be approved if the generic preparation of the drug is shown to be bioequivalent,⁴¹ in terms of its pharmacological properties, to the patented drug.⁴² ANDA approved (generic) drugs are then listed in the FDA “Orange Book,”⁴³ and can be marketed and sold by the generic company.

The safe harbor protection that Congress provided for generic drug-producing companies via 35 U.S.C. § 271(e)(1) was designed to eliminate the lag period between expiration of a CoM patent on a drug, and the introduction of a generic version of that drug into the market via ANDA approval. But is this safe harbor protection limited only to development of generic drugs, or can it be viewed more broadly, to include other areas of drug development research on patented drugs?⁴⁴ The courts have generally opted for the latter more

38. 35 U.S.C.A. § 271(e)(1) (West 2006).

39. *Id.*

40. *Abbreviated New Drug Application (ANDA): Generics*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm> (last updated July 17, 2013).

41. 21 C.F.R. § 320.1(e) (1977) (defining bioequivalent).

42. Such studies typically require demonstration that the “generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use.” *Abbreviated New Drug Application (ANDA): Generics*, *supra* note 40.

43. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN., <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm> (last updated May 17, 2013).

44. See Paul T. Nyffeler, *The Safe Harbor of 35 U.S.C. § 271(e)(1): The End of Enforceable*

expansive view of the safe harbor protection.⁴⁵

B. Statutory Interpretation and Common Law

In the years since Congress passed the “Hatch-Waxman Act,” the courts have expanded the scope of the safe harbor protections afforded by 35 U.S.C. § 271(e)(1), as a result of a number of Supreme Court cases, including several mentioned in this comment; and other cases may be on the horizon. This comment focuses on the implications of this expanded scope of the safe harbor protection for research directed toward repurposing drugs where the CoM protection is owned by someone else. Before discussing how the scope is expanding, some history, including legislative history of the statute itself, is provided. It all began with *Roche v. Bolar*.⁴⁴

1. Creation of 35 U.S.C. § 271(e)(1)

In *Roche v. Bolar*, Roche held a patent⁴⁶ on the sleeping pill Dalmane.⁴⁷ Bolar Pharmaceuticals sought to prepare a generic form of Dalmane, and thus needed to perform studies and gather data, such as “stability data, dissolution rates, bioequivalency studies, and blood serum studies,” that were expected to take about two years before they anticipated FDA approval for their generic form of the drug.⁴⁸ Bolar began performing studies six months before the Roche patent expired,⁴⁹ obtaining the drug compound for their studies from a foreign manufacturer. Bolar argued that not allowing them to pursue studies effectively gave Roche a *de facto* patent term extension.⁵⁰

While a patent clearly grants the patent holder the “right to exclude others from making, using, offering for sale, or selling the invention throughout the United States”⁵¹ the courts have recognized safe harbor protections against claims of patent-infringement. Ultimately, the U.S. Court of Appeals for the Federal Circuit held that Bolar infringed on Roche’s patent, however, the court also recognized that there was an effective *de facto* patent term extension, and therefore, the court encouraged Congress to address this problem and “rewrite

Biotechnology Patents in Drug Discovery?, 41 U. RICH. L. REV. 1025 (2007) (exploring the theory that Congress intended the broader view that other areas of drug discovery and development research, such as preclinical studies of alternative therapeutic uses (i.e. repurposing), fall under the protection of this safe harbor).

45. *Id.*

46. U.S. Patent No. 3,299,053 (filed Feb. 11, 1964) (expired Jan. 17, 1987).

47. *Roche Products, Inc. v. Bolar Pharm. Co., Inc.*, 733 F.2d 858 (Fed. Cir. 1984).

48. *Id.* at 860.

49. ‘053 Patent.

50. *Roche Prod., Inc. v. Bolar Pharm. Co., Inc.*, 572 F. Supp. 255, 257 (E.D.N.Y. 1983).

51. 35 U.S.C.A. § 154(a) (West 2000).

the patent laws.”⁵² This led to the Hatch-Waxman Act⁵³ resulting in the 35 U.S.C. § 271(e)(1) safe harbor protection. One purpose of the Hatch-Waxman Act was to provide for “a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute.”⁵⁴ But, the language of the statute is quite broad:

It shall not be an act of infringement to make, use, offer to sell, or sell . . . a patented invention . . . solely for uses *reasonably related to the development and submission of information under a Federal law* which regulates the manufacture, use, or sale of drugs or veterinary biological products.⁵⁵

Thus, it is left to the courts to ultimately determine the scope of the safe harbor protection provided under § 271(e)(1). *Eli Lilly & Co. v. Medtronic Inc.*, was a first step in this direction.⁵⁶

2. *Eli Lilly v. Medtronic*: Setting the Stage for *Merck v. Integra*

Eli Lilly v. Medtronic provided an initial expansion of the scope of 35 U.S.C. § 271(e)(1), beyond allowing studies directed toward the submission of information to the FDA under the ANDA for generic drugs. Medtronic claimed they deserved an exemption for research on medical devices, if the research is “‘reasonably related to the development and submission of information’” to the FDA under the Federal Food, Drug, and Cosmetic Act (FDCA); the Court agreed.⁵⁷ As a result of this Supreme Court decision, the § 271(e)(1) safe harbor protection was extended beyond development of generic drugs, to include studies generating information to be submitted to the FDA for NDA approval of medical devices. This was a modest expansion in scope compared to that which was to come under *Merck v. Integra*, a landmark case for repurposing research, and described in the next section.

3. *Merck v. Integra*

Since the creation of the § 271(e)(1) safe harbor protection, companies in the business of developing generic drugs have had the freedom to begin studies

52. *Roche v. Bolar*, 733 F.2d at 865 (“it is not our job to apply laws that have not yet been written.”) (citing *Sony v. Universal Studios*, 464 U.S. 417, 456 (1984)).

53. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

54. H.R. Rep. No. 98-857, pt. 2, at 8 (1984).

55. 35 U.S.C.A. § 271(e)(1) (emphasis added).

56. 496 U.S. 661 (1990).

57. *Id.* at 665–669 (citing 35 U.S.C. § 271(e)(1) (2006)).

of drugs owned by another party, even before that patent expired. This safe harbor protection was dramatically extended in 2005,⁵⁸ as a result of the landmark decision in *Merck v. Integra*.⁵⁹ Integra Lifesciences sued competitor Merck KGaA and an academic research institute, the Scripps Research Institute, for patent infringement and inducement to commit patent infringement. The issue was whether pre-clinical studies of patented drug molecules are protected under the § 271(e)(1) safe harbor. The Court held that they were protected, so long as there is a “reasonable basis” for believing that the research could generate the kind of information that is needed for an FDA filing, such as an IND or NDA. Given the importance of the *Merck* decision in expanding the scope of the safe harbor protection, and its implications for drug repositioning research and development, an extensive analysis of the Scalia decision is now presented.

a. The facts in Merck v. Integra

The Burnham Institute and Integra Lifesciences I, Ltd. (Integra) owned a series of patents on the arginine-glycine-aspartate tripeptide, referred to as RGD in single-letter notation.⁶⁰ In 1988, Merck KGaA (Merck) funded a researcher at the Scripps Research Institute (Scripps), Dr. David Cheresh, to perform studies on angiogenesis, the process by which blood vessels sprout from existing vessels.⁶¹ In the process of doing this research, Dr. Cheresh discovered a way to “inhibit angiogenesis . . . reversing tumor growth in chicken embryos, first using a monoclonal antibody (LM609) he developed himself and later using a cyclic RGD peptide (EMD 66203) provided by [Merck].”⁶² In 1995, Merck expanded its funding of this research, providing \$6 million over three years, to perform “toxicology tests necessary for FDA approval to proceed to clinical trials.”⁶³ Dr. Cheresh did various studies on the RGD peptides provided by Merck, focusing on EMD 66203, but also on derivatives EMD 85189 and EMD 121974. These studies focused on measuring “efficacy, specificity, and toxicity of the particular peptides as angiogenesis inhibitors.”⁶⁴

58. Nyffeler, *supra* note 44.

59. *Merck KGaA, v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005).

60. U.S. Patent No. 4,988,621 (filed Dec. 10, 1987); U.S. Patent No. 4,792,525 (filed June 17, 1985); U.S. Patent No. 5,695,997 (filed June 2, 1995); U.S. Patent No. 4,879,237 (filed May 24, 1985); U.S. Patent No. 4,789,734 (filed Aug. 6, 1985).

61. *Merck*, 545 U.S. at 197.

62. *Id.*

63. *Id.* at 198 (citation omitted); *see also* 21 C.F.R. § 312.23(a)(8)(iii) (regarding nonclinical laboratory studies).

64. *Merck*, 545 U.S. at 198–199.

Based on Dr. Cheresch's research results, Scripps decided to pursue EMD 121974 as a drug candidate for testing in humans, and continued to use RGD peptides as "positive controls."⁶⁵ Likewise, Merck decided to move RGD peptides through the regulatory approval process with the FDA, focusing first on EMD 85189, and then on EMD 121974; Merck also discussed the possibility of sponsoring a human clinical trial with the National Cancer Institute (NCI).⁶⁶ Accordingly, NCI filed an Investigative New Drug (IND) application in 1998, to move this compound into human clinical trials.⁶⁷

b. The issue of safe harbor protection scope

In 1996, Integra filed a patent-infringement suit against Merck, Scripps, and Dr. Cheresch, for infringing its RGD peptide patents.⁶⁸ While the District Court held that the "pre-1995 actions related to the RGD peptides were protected by the common-law research exemption,"⁶⁹ a question remained as to whether the use of the patented RGD peptides by Merck and Scripps, after 1995, fell within the § 271(e)(1) safe harbor exemption.⁷⁰ While the District Court ruled that the safe harbor protection did not reach this far, the Court of Appeals affirmed in part and reversed in part.⁷¹ Ultimately, the Supreme Court vacated the judgment and remanded, holding that "the use of patented compounds in pre-clinical studies is protected under § 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce 'the types of information that are relevant to an IND or NDA.'"⁷²

c. Scope includes research directed to IND and NDA filing

Under this more expansive interpretation of § 271(e)(1), studies on patented compounds are not considered infringement, as long as they are directed toward the filing of FDA regulatory documents, in particular an IND (to enter human clinical trials) or NDA (to enter the market). To qualify for safe harbor protection, the studies must be "reasonably related" to the "development and submission of any information" to the FDA," which has now been specified as being "information that [is] relevant to an IND or NDA."⁷³ But, what kind of information is "relevant to an IND or NDA"?

65. *Id.* at 199 (citation omitted).

66. *Id.*

67. *Id.*

68. *Id.* at 200.

69. *Id.*

70. *Id.*

71. *Id.* at 201.

72. *Id.* at 208.

73. *Id.* at 207–08 (citation omitted).

d. The scope of the safe harbor protection extends beyond safety studies

Integra argued that 35 U.S.C. § 271(e)(1), only provided safe harbor protection for pre-clinical studies of drug safety, not studies of “a drug’s efficacy, mechanism of action, pharmacokinetics, and pharmacology,” since such data is “not reasonably included in an IND or an NDA.”⁷⁴ While it is conceded that the FDA’s “primary objectives in reviewing an IND are . . . to assure the safety and rights of subjects,”⁷⁵ the Court concluded that the FDA’s interest could not be constrained so narrowly as to only consider safety. Rather, the Court concluded that the “FDA requires that applicants include in an IND, summaries of the pharmacological, toxicological, pharmacokinetic, and biological qualities of the drug in animals.”⁷⁶ Thus, the § 271(e)(1), safe harbor protection can now be construed more expansively to also cover the following pre-clinical studies of a patented drug: (a) pharmacology, (b) toxicology, (c) pharmacokinetics, and (d) biological qualities that are of relevance to FDA filings. But what happens if such FDA filings never occur?

e. Scope not limited to studies included in IND, NDA or ANDA filings

The Court further concludes that the § 271(e)(1) protection does not exclude “experimentation on drugs that are not ultimately the subject of an FDA submission,”⁷⁷ such as an IND, NDA, or ANDA filing. While basic research on a patented compound, “without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect,”⁷⁸ is not protected by the safe harbor exclusion, research is allowed as long as it is “reasonably related to the development and submissions of information to the FDA,” even if that information is never submitted to the FDA.⁷⁹ Therefore, the § 271(e)(1) safe harbor protection “leaves adequate space for experimentation and failure on the road to regulatory approval,”⁸⁰ and in fact recognizes that most pre-clinical studies do not result in FDA regulatory filings or approvals, even though that may have been the intent of the studies. Thus, all that is required of the researcher is “a reasonable basis for believing that a patented compound may work”⁸¹ in clinical studies; however, there is no requirement that the compound ever become the subject of a clinical study, or an FDA filing.

74. *Id.* at 203.

75. *Id.* (quoting 21 C.F.R. § 312.22(a) (2005)).

76. *Id.* at 72.

77. *Id.* at 206.

78. *Id.* at 205–06.

79. *Id.* at 206.

80. *Id.* at 207.

81. *Id.*

4. After Merck v. Integra

In *Classen v. Biogen Idec*,⁸² Classen owned patents that claimed methods for immunizing, which they claimed that Biogen, IDEC, and GlaxoSmithKline (GSK) infringed during their post-approval (i.e. after NDA approval, when the drug is on the market) studies of “‘associations between childhood vaccinations . . . and [the] risk of developing type I diabetes.’”⁸³ The issue was whether the safe harbor protection extended to these studies, which were not directed to ANDA approval, and occurred after a drug had already been approved. Biogen, IDEC, and GSK argued that their activities were protected by the § 271(e)(1) safe harbor, because those types of safety studies were required by the FDA under 21 C.F.R. § 601.70 and § 600.80, in order to report “adverse events” for drugs to the FDA. The court held that the safe harbor protection does not extend to post-approval studies of drug-induced “adverse events,” but the court was silent on the broader issue of other post-approval activities on patented drugs.

Citing legislative history, the Federal Circuit court claimed that the legislative intent for the § 271(e)(1) safe harbor protection was to shorten the time for generic drug approval, a pre-market activity.⁸⁴ The court stated that “every decision examining the statute has appreciated that § 271(e)(1) is directed to premarketing approval of generic counterparts before patent protection.”⁸⁵ The court ultimately held in a 2–1 decision that the safe harbor “does not apply to information that may be routinely reported to the FDA, long after marketing approval has been obtained.”⁸⁶ This decision was appealed, and a petition for certiorari was submitted, but certiorari ultimately denied (see below). This decision could be viewed as a contraction of the safe harbor protection that is not supported by the plain language of the statute, which makes no mention of being limited to “pre-approval” research activities on drugs.

Based upon a recommendation of the Solicitor General,⁸⁷ on January 14, 2013, the Supreme Court denied GSK’s petition for certiorari.⁸⁸ The Solicitor

82. *Classen Immunotherapies, Inc. v. Biogen Idec*, 659 F.3d 1057 (Fed. Cir. 2011).

83. *Id.* at 1070 (quoting *Classen Immunotherapies, Inc. v. Biogen IDEC*, 381 F. Supp. 2d 452, 455 (D. Md. 2005)).

84. *Id.* at 1070.

85. *Id.* at 1071.

86. *Id.* at 1070.

87. Brief for the United States as Amicus Curiae, *GlaxoSmithKline v. Classen Immunotherapies, Inc.*, 133 S. Ct. 50 (2012) (No. 11-1078).

88. *Supreme Court Declines Opportunity to Clarify Scope of Hatch-Waxman Safe Harbor*, JDSUPRA LAW NEWS (Jan. 17, 2013), <http://www.jdsupra.com/legalnews/supreme-court-declines-opportunity-to-cl-38040/>.

General described the Federal Circuit’s limitation of the safe harbor protection in *Classen* as “misguided” and urged that nothing in the text of the statute “warrants the court of appeals’ categorical exclusion of post-approval activity from the safe harbor.”⁸⁹ Rather, the Solicitor General supported the narrow interpretation of *Classen*, provided in the *Momenta v. Amphastar* decision.⁹⁰ Thus, the constraint on the scope of the § 271(e)(1) safe harbor protection that *Classen* might have introduced, limiting it to “pre-approval” research, has now been reigned in.

In *Momenta v. Amphastar*, the court did allow safe harbor protection beyond just pre-approval activities.⁹¹ There, *Momenta* held a method patent (the ‘886 patent) for “analyzing heterogeneous populations of polysaccharides,”⁹² and also had FDA approval to market the generic form of the drug. Later, *Amphastar* also received FDA approval for its generic form of the same drug. *Momenta* sued *Amphastar* for infringing its ‘886 patent, claiming *Amphastar* used their method.⁹³ The question here is whether § 271(e)(1) safe harbor protection for generic drug manufacturers continues even after they receive ANDA approval for their drug. In other words, the question is, as it was in *Classen*, whether safe harbor extends to the post-approval period. However, unlike in *Classen*, the court concluded that § 271(e)(1) safe harbor protection can extend beyond pre-approval research activities, to include some post-approval studies.⁹⁴ The Court distinguished *Classen* by noting that in this case, the post-approval activities were necessary to satisfy FDA requirements, whereas in *Classen* the activities in question were just routine activities.⁹⁵ Thus, *Momenta* stands for an expansion of the § 271(e)(1) safe harbor protection, beyond just pre-approval activities. However, due to constraints imposed by the *Classen* decision, that expansion does not occur if the activities are “routine” and not directed towards obtaining FDA approval or satisfying FDA requirements. The dissent argues that this decision “would essentially render manufacturing method patents worthless.”⁹⁶

89. Brief for the United States, *supra* note 87, at 12.

90. *Id.* at 10.

91. *Momenta Pharm., Inc. v. Amphastar Pharm., Inc.* 686 F.3d 1348 (Fed. Cir. 2012)

92. U.S. Patent No. 7,575,886 B2 (filed Mar. 11, 2003).

93. *Momenta Pharm.*, 686 F.3d at 1352.

94. *Id.* at 1359 (holding that “post-approval studies that are ‘reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs’ fall within the scope of the . . . safe harbor.”).

95. *Id.* at 1352 (holding that “[t]he [safe harbor] does not apply to information that may be routinely reported to the FDA long after marketing approval has been obtained.”).

96. *Id.* at 1369.

C. Summary of Current Law the Legal Issue

The scope of the § 271(e)(1) safe harbor protection for research on patented drugs has expanded under *Merck* and subsequent cases like *Momenta*. Based on the plain language of the statute, legislative history, and case history, the current scope of the protection requires that studies be “reasonably related to the development and submission of any information”⁹⁷ to the FDA, and that the “information [is] relevant to an IND or NDA.”⁹⁸ But, studies that are performed on the drug compound do not have to yield positive results, and do not have to actually result in an FDA filing. All that is required is that the researcher had “a reasonable basis for believing that a patented compound may work” in clinical studies.⁹⁹ Furthermore, the recent decision in *Momenta*, which reigned in a potential constraint by *Classen*, extends the safe harbor protection beyond pre-approval studies, as long as they are more than “routine studies” such as reporting adverse events to the FDA. The legal issue is, as it has been since the passage of the Hatch-Waxman Act, defining the boundaries of the safe harbor protection provided by § 271(e)(1) against patent infringement suits; but, with each year the courts are providing more clarity on this point, and are helping to guide our interpretation of the statutory language: “reasonably related to the development and submission of any information” to the FDA.¹⁰⁰

IV. APPLYING THE LAW TO DRUG REPURPOSING

The above analysis of case history and legal precedent provides some clarity as to the scope of the § 271(e)(1) safe harbor protection, in a broad sense. But, how are these guidelines applied specifically to research that is directed toward finding new uses for patented drugs that are currently on the market? That is, to what extent does the § 271(e)(1) safe harbor protection permit repurposing research performed by non-patent owners, including researchers in universities and small companies?

A. Repurposing Research

To repurpose a drug, a scientist must demonstrate that an existing drug, known to be useful for treating *Disease A*, is also useful for treating *Disease B*. Of course, if a researcher would like to patent this new use, then the new use must not have been obvious to someone of ordinary skill in the field. To discover this new use, with the intention of someday performing clinical studies

97. *Merck KGaA, v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 193 (2005).

98. *Merck*, 545 U.S. at 208.

99. *Id.* at 207.

100. *Id.* at 193.

in humans, researchers must first do a number of tests *in vitro*. For example, they might demonstrate that the drug that is patented for treating *Disease A* binds to new proteins that it was not known to bind to, where binding to those new proteins is reasonably expected to be efficacious for treating a new disease, *Disease B*. Or, experiments might be performed in animal disease models for *Disease B*, where a *Disease B* therapeutic benefit is discovered that was not anticipated. While both types of studies are directed toward developing a drug, and therefore to filing an IND with the FDA, science is notoriously unpredictable and it is not known at the outset if such a filing will occur.

The legal rules extracted from the above analysis do not actually require that an FDA filing ultimately occurs, in order for a repurposing researcher to be protected under the § 271(e)(1) safe harbor. What does matter is that the researcher must have had “a reasonable basis for believing a compound may work” in the pre-clinical and (later) clinical studies associated with the new use, treating *Disease B* with the drug designed for treating *Disease A*. It does not matter whether an IND or NDA is ever filed.

Besides demonstrating drug efficacy for *Disease B*, a repurposing researcher may need to demonstrate that administering the drug, as it would need to be administered for *Disease B*, is also safe. Related to safety, repurposing researchers may also need to perform pharmacokinetic studies in animal models, explore different drug formulations, develop improved ways to manufacture the drug, measure drug stability, and perform analytical characterizations, along with other studies that are sometimes required by the FDA in IND filings. All of these studies should be protected under the § 271(e)(1) safe harbor, within the boundaries defined in the next sections, as a result of the *Merck* and *Momenta* decisions.

B. Implications of Merck and Momenta (M&M) for Repurposing Research

Under *Merck*, the safe harbor protection extends to research “reasonably related to the development and submission of any information under the FDA,” which would include information needed to file an IND or AND, as long as they “are appropriate for submission to the FDA in the regulatory process.”¹⁰¹ This excludes basic research on patented drugs; but, repurposing is not basic research. Rather, repurposing research is directed to finding new uses for existing (typically patented) drugs, with plans to enter that drug into clinical trials after an IND or AIND is filed with the FDA. Therefore, because repurposing research is, by its very nature, focused on developing a drug which requires FDA filings, it would typically fall under the § 271(e)(1) safe harbor.

Exactly what kind of repurposing research is allowed under the safe harbor

101. *Id.* at 203.

protection? While the plaintiff in *Merck* argued that research activities needed for an IND were narrow and did not include safety, “efficacy, mechanism of action, pharmacokinetics, and pharmacology . . . [the court held that] the FDA’s interest in information gathered in preclinical studies [was not] so constrained. . . . [and that the FDA] requires that applicants include in an IND summaries of the pharmacological, toxicological, pharmacokinetic, and biological qualities of the drug in animals.”¹⁰² These are exactly the types of studies that a scientist looking to repurpose a drug would need to perform, and which are protected under the safe harbor protections of § 271(e)(1), as interpreted in *Merck*. The Court agreed that basic research on a patented drug is not protected under § 271(e)(1) if: (1) there is no intent to develop a particular drug, or (2) there is no “reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce.”¹⁰³ But, repurposing is about developing a drug, and researchers would not pursue a repurposing project unless they had a “reasonable belief” that the drug would have the desired biological effect.

What if a repurposing researcher had a “reasonable belief” that a drug would work for a new disease indication, but that researcher was ultimately mistaken, and no FDA filings ever get submitted? To obtain safe harbor protection, it is not essential that the researcher’s experiments produce data that are used in the FDA filing (e.g. an IND). Rather, the researcher just needs to have had “a reasonable basis for believing the experiments will produce the ‘types of information relevant to an IND or NDA.’”¹⁰⁴ Since *Momenta* has now extended the safe harbor protection beyond research performed before IND and NDA filings, to include post-approval activity (after NDA), it is now a smaller stretch to infer that the protection also covers research directed towards AIND and ANDA filings—whereby one is simply amending an existing IND or NDA. If post-approval activities are permitted, then it seems likely that most pre-approval activities that could result in FDA filings would be permitted. Thus, the safe harbor protection offered by § 271(e)(1) seems to permit researchers, whether in companies or universities, to undertake repurposing projects that are being pursued in good faith, with “reasonable” expectations of someday filing an IND, AIND, NDA, or ANDA, even if one does not ultimately include data from the studies in that filing, and even if one never actually makes such a filing.

Of course, some ambiguities remain. What is meant by “reasonably believe”? Does the researcher need to demonstrate “intent to develop a

102. *Id.*

103. *Id.* at 206.

104. *Id.* at 208.

particular drug,” towards the goal of submitting FDA regulatory documents, in order to claim safe harbor protection for their research on patented drugs; and how would intent be demonstrated? Furthermore, what does “reasonably related to the development and submission of information” mean? Can a scientist screen patented drugs against a panel of proteins, fishing for a new disease indication? Such a scenario seems too far removed from a reasonable expectation of finding clinical benefit that could lead to an FDA filing; but a repurposing researcher would not perform those studies unless they had a belief that they could result in a new use for the drug. The boundaries of this “reasonable belief” threshold have yet to be defined. Presumably these ambiguities will be resolved as the case law continues to evolve. But, on the face of what repurposing is commonly understood to mean by those skilled in the art, there appears to be considerable freedom to operate.

C. Public Policy Considerations for Repurposing Research

1. Society Needs New Medicines – Repurposing Serves the Greater Social Good

This comment argues that pre-clinical (i.e. before IND filing; before human studies) and clinical (i.e. after IND; in humans) drug repurposing studies on patented compounds are generally permitted. The courts have already spoken on this matter, and it is now the law. But, since the scope of the safe harbor protection has been expanding, and may continue to expand, it is important to ask whether the safe harbor protection of repurposing research is in the public interest? The answer to this question may provide some guidance as the courts continue to navigate the extent to which this scope should be expanded.

As pharmaceutical companies’ pipelines of new drug products dwindle, the need for new therapeutics is increasing, and human suffering due to unmet medical needs continues unabated. If there are existing but unrecognized ways to treat these problems, why not facilitate the discovery of these new therapeutic strategies? Some might argue that it is not innovative to find a new use for a drug molecule when some other company designed that drug molecule. But, as pharma faces the huge financial losses associated with “patent cliffs”¹⁰⁵ resulting in massive layoffs,¹⁰⁶ it is hard to imagine that there is not an adequate incentive and opportunity for them to identify new uses for their drugs that are about to lose CoM patent protection.

It is possible that a large pharmaceutical company may have known or suspected new and alternative uses for their patented drug in some cases, but

105. Harrison, *supra* note 8.

106. Carroll, *supra* note 9.

decided not to explore the less financially lucrative new uses, such as treating rare or neglected diseases. Is it fair then, that such diseases go untreated when a drug may exist, but these alternative uses were not explored because they could not generate the level of revenue needed to sustain the large company that owns the patent? For many years pharma operated under a “blockbuster” drug model, where they generally only pursued diseases with a market potential of more than \$1 billion per year. Why would they pursue an alternate use for such a drug to treat a rare disease (defined as less than 200,000 people) when any liabilities identified for that alternative use would put the larger market use at risk? Furthermore, why would large pharma pursue small markets that provide such a small fraction of the revenues they need to sustain their large infrastructure? Resources are typically allocated to projects with a larger potential market. It serves the greater social interest in health care, and the useful art of medicine, to allow smaller companies and academic researchers to explore these financially less lucrative alternative uses for patented drugs, under the safe harbor protection.

Finally, in situations where CoM patents are close to expiring, companies may avoid exploring these new uses because they view MoU patents as being weaker than CoM patents. They may also have an unfavorable view on granting a MoU patent on a new use for a molecule that has CoM protection. However, it seems only fair, and serves the greater public good, to allow other researchers to explore new uses for these drug molecules, which the original patent owner might have overlooked or intentionally not explored for strategic business reasons. In any case, the CoM patent owner will have had twenty years to recoup their R&D investment, so it can hardly be viewed as unfair if someone else finds a new use that the original CoM patent owner could not uncover due to the lack of insight or ability, or would not explore due to the lack of financial incentive. In all of these scenarios, a potential cure or treatment is going unrecognized and unused, which clearly is not serving the greater social good. If a repurposing scientist finds a new use for a patented drug, and a new therapeutic intervention emerges where before there was previously none, there is clearly social good. Is there a corresponding harm to the original owner of the CoM patent that is about to expire when they had failed to recognize that new use themselves? That is arguable. Perhaps in some cases yes; but in most cases the answer is more likely to be no.

2. From Fairies to Financial Bias

Should academic researchers be allowed to perform repurposing-based drug development? *Merck v. Integra* and subsequent cases have expanded the scope of safe harbor protections, which will enable academic drug discovery researchers, typically funded by the NIH, to now pursue drug repurposing

studies. This is not without controversy. The former CEO of Merck, Dr. Roy Vagelos, testified before Congress and advised them not to permit this kind of research, stating that “such studies that are aimed at obtaining additional claims for drugs already being sold should be funded by the company that owns the drug and will benefit financially from the additional claim.”¹⁰⁷ While Dr. Vagelos has impressive credentials in drug development, he is hardly an unbiased voice to guide Congress on what biomedical research they should be funding through the NIH. Clearly, any pharmaceutical company would like to “benefit financially from the additional claim” for new uses for their patented drugs, but if the creative insights of another scientist are what uncovers the new use, then it is not the original CoM patent owner that should be further rewarded for that innovation. If a pharmaceutical company had CoM protection for twenty years, and has not yet discovered new uses for their drug, it seems like it is time to let some other innovative researcher discover a new use and reap the benefit for their insights and hard work.

3. Innovation – To Advance Science and the Useful Arts – Such as Medicine

What is innovation? Merriam-Webster defines innovation as “the introduction of something new,” and “a new idea, method, or device.”¹⁰⁸ In patent law, it can be considered novel to have a new use for an existing composition of matter. That is, in fact, one distinction between composition of matter (CoM) and method or process patents. Thus, it seems to authentically innovative to discover and implement a new use for a molecule. Again, the fact that there is untapped potential for financial gain by a current CoM patent-holder that went unrecognized is evidence that it was not easy or routine to uncover the new use for their patented molecule. Thus, it can be argued that repurposing is innovative and finding a new use is indeed a scientific discovery that can be put to good use, and perhaps even commercialized. The Constitution specifically rewards such innovation and the application of that innovation through the patent clause, which has the stated purpose “[t]o Promote Science and the Useful Arts.”¹⁰⁹ Finding a new use for a drug is a scientific discovery and thus advances science. It also provides a new therapeutic intervention that physicians can use that clearly advances the useful art of medicine and has significant and positive social impact.

107. *Budget Hearing of the Dep’t of Health and Human Services*, *supra* note 13.

108. *Innovation definition*, MERRIAM-WEBSTER.COM, <http://www.merriam-webster.com/dictionary/innovation> (last visited Nov. 29, 2013).

109. U.S. CONST. art. I, § 8, cl. 8.

V. CONCLUSION

The scope of the § 271(e)(1) safe harbor protection for research on patented drugs has expanded significantly under *Merck v. Integra*. It would permit most repurposing, repositioning, and rescuing research, which is pre-clinical research focused on drug development, preparing a drug lead molecule for entry into clinical trials. The types of pre-clinical studies allowed under the safe harbor umbrella include characterization of a patented drug's: (a) pharmacology, (b) toxicology, (c) pharmacokinetics, and (d) biological qualities. To qualify for safe harbor protection, repurposing studies on patented drugs must be "reasonably related to the development and submission of any information" to the FDA, or "information that are relevant to an IND or NDA." All that is required is that the researcher have "a reasonable basis for believing a compound may work" in clinical studies, but there is no requirement that the compound necessarily be the subject of an FDA filing. Thus, repurposing studies are largely protected from patent infringement suits under the § 271(e)(1) safe harbor protections created by the Hatch-Waxman Act. The fact that such studies are permitted is in the public interest, serves the social goal of improving public health, and rewards innovation, while also advancing science and the useful arts.

It is good that the NIH is funding drug development and repurposing studies as a complement to industrial drug development initiatives, since big pharma has become a less reliable source of new medicines in recent years. This will be a challenging undertaking for academic labs, but there is no reason to believe they cannot rise to the challenge. While it is insanity to believe in fairies, it is also "insanity to keep doing the same thing over and over again and expect different results."¹¹⁰ Quite simply, we need new medicines, and big pharma's ability to address this need is decreasing. It is time to try a new model, one that involves academic-industrial partnerships, encourages drug repurposing, and is more open to the pursuit of rare and neglected diseases.

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110. Attributed to Albert Einstein. BRAINYQUOTE.COM, <http://www.brainyquote.com/quotes/quotes/a/alberteins133991.html>.

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