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## FIVE SOLUTIONS TO THE REMS PATENT PROBLEM

MICHAEL A. CARRIER\* & BRENNA SOOY\*\*

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*Two principles collide in the pharmaceutical industry. On the one hand, the U.S. Food and Drug Administration (“FDA”) approves potentially dangerous drugs under Risk Evaluation and Mitigation Strategies (“REMS”) programs when a drug’s benefits outweigh its risks. But on the other hand, brand firms can prevent generic competition by patenting these programs.*

*REMS patents, which claim compliance with FDA-imposed REMS programs, pose two problems—one procedural, the other substantive. First, current practice is to list REMS patents in the Orange Book even though such listings may be invalid, with this conduct allowing the brand to obtain an automatic 30-month stay of generic approval. Second, because a REMS program appears on a product’s label and generics must copy that label, REMS patents threaten generics with claims of induced infringement.*

*We offer five solutions to these problems. First, we target brands’ listings of REMS patents in the Orange Book, proposing that generic firms sued for infringement file counterclaims to delist REMS patents and that the FDA issue guidance making clear that REMS patents cannot be listed. Second, we suggest more rigorous scrutiny of REMS patents in the courts and at the U.S. Patent and*

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\* Distinguished Professor, Rutgers Law School.

\*\* 3L, Rutgers Law School. We would like to thank Mark Lemley, Erika Lietzan, Michael Risch, and Jay Thomas for very helpful comments. Copyright © 2017 Michael A. Carrier & Brenna Sooy.

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*Trademark Office. Third, we apply the Supreme Court's four-factor eBay test to conclude that courts should award damages rather than injunctions in cases of infringement. Fourth, we suggest that Congress amend the Food and Drug Administration Amendments Act of 2007 to mitigate the effects of REMS patents. And fifth, we recommend that, similar to the treatment of tax-strategy patents in the America Invents Act, Congress deem REMS patents to fall within the prior art.*

#### INTRODUCTION

Two principles collide in the pharmaceutical industry. On the one hand, the U.S. Food and Drug Administration ("FDA") approves potentially dangerous drugs under Risk Evaluation and Mitigation Strategies ("REMS") programs when a drug's benefits outweigh its risks.<sup>1</sup> But on the other hand, brand firms can prevent generic competition by patenting these programs.

REMS patents, which claim compliance with FDA-imposed REMS programs, pose two problems—one procedural, the other substantive. First, current practice is to list REMS patents in the Orange Book *even though such listings may be invalid*. This behavior has significant consequences as the listing allows the brand to obtain an automatic 30-month stay of generic approval. Second, because a REMS program appears on a product's label<sup>2</sup> and generics must copy that label,<sup>3</sup> REMS patents threaten generics with claims of induced infringement. As a result, the generic will typically infringe the REMS patent.

We offer five solutions to this problem. First, we target brands' listings of REMS patents in the Orange Book. Statutory provisions and FDA regulations make clear that REMS patents do not fall within the categories of patents that can be listed because they do not claim a drug or method of using a drug.<sup>4</sup> We recommend that generic firms, after being sued for patent infringement, file counterclaims to delist REMS patents. We also propose that the FDA issue guidance making clear that REMS patents cannot be listed in the Orange Book.

Second, we suggest more rigorous scrutiny of REMS patents in the courts and at the U.S. Patent and Trademark Office ("PTO"). We explore options that the America Invents Act<sup>5</sup> ("AIA") made available, such as *inter partes* review

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<sup>1</sup> 21 U.S.C.A. § 355-1(a)(1) (West 2017).

<sup>2</sup> See Linda Pissott Reig & James F. Hlavenka, *Risk Evaluation and Mitigation Strategies (REMS) and Related Post-Market Safety Oversight*, in PHARMACEUTICAL COMPLIANCE AND ENFORCEMENT ANSWER BOOK 285, 292, Bloomberg BNA (2017).

<sup>3</sup> 21 U.S.C.A. § 355(j)(2)(A)(v) ("An abbreviated application for a new drug shall contain . . . information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers . . .").

<sup>4</sup> *Id.* § 355(b)(1).

<sup>5</sup> Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (codified as amended in scattered sections of 28, 35, and 51 U.S.C.).

(“IPR”) and covered business method (“CBM”) review, and we examine challenges that raise significant concerns based on patentable subject matter and obviousness. Such challenges are particularly likely to be successful because most REMS patents in force today were prosecuted before the landmark Supreme Court decision in *Alice Corp. v. CLS Bank International*,<sup>6</sup> which limited patentable subject matter.<sup>7</sup>

Third, we apply the four-factor test the Supreme Court articulated in *eBay Inc. v. MercExchange, L.L.C.*,<sup>8</sup> for assessing whether courts should award injunctions in cases of infringement.<sup>9</sup> We conclude that the outcome on the irreparable-harm factor is mixed but the other three factors counsel against an injunction because the adequacy of damages, balance of hardships, and public interest all favor monetary damages.

Fourth, based on the role REMS patents play in the regulatory system, the limited need for the patents, and the significant potential that such patents will block generic entry, we recommend that Congress mitigate REMS patents through amendments to the Food and Drug Administration Amendments Act of 2007 (“FDAAA”).<sup>10</sup> And fifth, we recommend, similar to the treatment of tax-strategy patents in the AIA, that Congress deem REMS patents to fall within the “prior art.”

Each of these five solutions offers unique benefits. The first addresses the inappropriate 30-month bottleneck that arises from listing patents in the Orange Book. The second promises to root out invalid patents. The third incorporates policies at the heart of the regulatory regime by recommending damages rather than injunctions. And the fourth and fifth apply more global approaches that incorporate the lack of need for REMS patents and severe anticompetitive threats they pose. In short, the five solutions offer the hope of reconciling generic competition and REMS patents.

## I. REGULATORY BACKGROUND

As much as any setting, the pharmaceutical industry is characterized by a complex regulatory regime. This Part introduces two of the leading components: the Hatch-Waxman Act<sup>11</sup> and the FDAAA.

### A. *The Hatch-Waxman Act*

The Hatch-Waxman Act created a comprehensive scheme governing pharmaceutical competition and innovation. At the time Congress enacted the

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<sup>6</sup> 134 S. Ct. 2347 (2014).

<sup>7</sup> *Id.* at 2357.

<sup>8</sup> 547 U.S. 388 (2006).

<sup>9</sup> *Id.* at 391.

<sup>10</sup> Pub. L. No. 110-85, 121 Stat. 823 (2007) (codified as amended at 21 U.S.C. § 355-1).

<sup>11</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355).

Act in 1984, there was no generic equivalent for roughly 150 drugs whose patent terms had lapsed.<sup>12</sup> Spurring generic competition was an explicit goal of the Hatch-Waxman Act. Looking at the marketplace, the drafters sought to ensure the provision of “low-cost, generic drugs for millions of Americans.”<sup>13</sup> The drafters also believed the legislation would “do more to contain the cost of elderly care than perhaps anything else this Congress has passed.”<sup>14</sup> A crucial centerpiece of the Act, in short, involved a reduction in drug prices by facilitating generic entry.<sup>15</sup>

The Hatch-Waxman Act drafters encouraged generic challenges to invalidate patents or prove noninfringement, believing that such challenges would lead to earlier market entry and lower prices.<sup>16</sup> They exempted from infringement the manufacture, use, or sale of a patented invention for uses “reasonably related to the development and submission of information under a federal law which regulates the manufacture, use, or sale of drugs.”<sup>17</sup> Congress also granted a 180-day period of marketing exclusivity to the first generic to file a “paragraph IV”<sup>18</sup> challenge claiming that the patent is invalid or not infringed.<sup>19</sup>

In addition to providing pre-expiration testing and market exclusivity, the drafters allowed generics to avoid the new-drug-application (“NDA”) process by filing an Abbreviated New Drug Application (“ANDA”).<sup>20</sup> To do this, the generic manufacturer must show that its drug possesses the same active ingredient, route of administration, bioequivalence, and other characteristics as the branded drug.<sup>21</sup> If it can make this showing, the generic can rely on the brand’s safety and effectiveness studies, dispensing with the need to conduct lengthy and expensive clinical trials.<sup>22</sup> As the Supreme Court has confirmed, a central purpose of the Hatch-Waxman Act was to allow generics to “piggy-

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<sup>12</sup> H.R. REP. NO. 98-857, pt. 1, at 17 (1984), as reprinted in 1984 U.S.C.C.A.N. 2647, 2650, 1984 WL 37416; see also Michael A. Carrier, *Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality*, 108 MICH. L. REV. 37, 42 (2009).

<sup>13</sup> 130 CONG. REC. 24,427 (daily ed. Sept. 6, 1984) (statement of Rep. Henry Waxman).

<sup>14</sup> *Id.*

<sup>15</sup> Additionally, to foster innovation in the pharmaceutical industry, the Hatch-Waxman Act drafters used patent-term extensions, market exclusivity, and 30-month stays. See Carrier, *supra* note 12, at 43-45.

<sup>16</sup> *Id.* at 71.

<sup>17</sup> 35 U.S.C. § 271(e)(1) (2012).

<sup>18</sup> 21 U.S.C.A. § 355(j)(2)(A)(vii) (West 2017).

<sup>19</sup> *Id.* § 355(j)(5)(B)(iv).

<sup>20</sup> *Id.* § 355(j)(2)(A), (j)(2)(A)(i)-(viii).

<sup>21</sup> FED. TRADE COMM’N, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 5* (2002), <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf> [<http://perma.cc/3D3E-2CD3>].

<sup>22</sup> *Id.*

back[]” on the brand’s application, which would “speed the introduction of low-cost generic drugs to market.”<sup>23</sup>

The competition policies underlying the Hatch-Waxman Act were strengthened by state drug product selection (“DPS”) laws, now in effect in all 50 states.<sup>24</sup> These laws allow (and often require) pharmacists, absent a doctor’s contrary instructions, to substitute generic versions of brand drugs when filling prescriptions. The laws are designed to address the disconnect in the industry between prescribing doctors, who are not directly responsive to drug pricing, and paying insurers and consumers, who do not directly select the prescribed drug.<sup>25</sup> In particular, DPS laws carve out a role for pharmacists, who are much more sensitive to prices than doctors.<sup>26</sup>

For the most part, the Hatch-Waxman Act and state laws have been successful in increasing generic entry. Making up 19% of the prescription drug market in 1984, generics now constitute 89% of the market.<sup>27</sup> Generics enter the market at significantly lower prices, with an average cost that is 80-85% lower than that of a brand drug.<sup>28</sup> The comparatively low price of generics means that brand drugs, which make up only 11% of prescriptions today, are responsible for 73% of drug spending.<sup>29</sup> Between 2006 and 2015, the ten-year savings from generic drugs was nearly \$1.5 trillion.<sup>30</sup>

#### B. REMS Programs

Another relevant set of regulations more directly implicates REMS. In 2005, the FDA provided industry guidance for Risk Minimization Action Plans (“RiskMAPs”), a voluntary system by which drug sponsors implement plans to

<sup>23</sup> Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 566 U.S. 399, 408-09 (2012) (citing *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990)).

<sup>24</sup> Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1017-19 (2010).

<sup>25</sup> See BUREAU OF CONSUMER PROT., DRUG PRODUCT SELECTION: STAFF REPORT TO THE FEDERAL TRADE COMMISSION 2-3 (1979).

<sup>26</sup> ALISON MASSON & ROBERT L. STEINER, FED. TRADE COMM’N, GENERIC SUBSTITUTION AND PRESCRIPTION DRUG PRICES: ECONOMIC EFFECTS OF STATE DRUG PRODUCT SELECTION LAWS 7 (1985) (“[P]armacists must respond to consumer demand because of direct competition with other pharmacies on prescription prices.”).

<sup>27</sup> See GENERIC PHARM. ASS’N, 2016 GENERIC DRUG SAVINGS & ACCESS IN THE UNITED STATES REPORT 5 (2016) [hereinafter GPHA REPORT], <http://www.gphaonline.org/media/generic-drug-savings-2016/index.html> [https://perma.cc/92Y2-K88C].

<sup>28</sup> FDA, *Facts about Generic Drugs* (June 28, 2016), <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm> [https://perma.cc/YXC7-SH5L].

<sup>29</sup> GPHA REPORT, *supra* note 27, at 5.

<sup>30</sup> *Id.* at 6.

minimize risks.<sup>31</sup> A RiskMAP is “a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits.”<sup>32</sup> These were developed for products requiring strategies “beyond describing the risks and benefits of the product in labeling and performing required safety reporting”<sup>33</sup> and were the regulatory precursors to REMS.<sup>34</sup>

In 2007, Congress enacted the FDAAA.<sup>35</sup> Section 505-1(a)(1) of the Act authorizes the FDA to require drug application sponsors<sup>36</sup> to submit a proposed REMS if the agency determines that it is needed to ensure that a drug’s benefits outweigh its risks.<sup>37</sup> By September 2008, holders of drug applications that the FDA selected for REMS were required to submit proposed REMS programs.<sup>38</sup> The transition to mandatory REMS was not intended to significantly change the voluntary programs in place at the time.<sup>39</sup>

The FDA has defined REMS as “required risk management plans that use risk minimization strategies beyond . . . professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks.”<sup>40</sup> Examples of REMS requirements include education addressing possible risks of serious infection, certification and training of prescribers and dispensers, continued monitoring for liver damage, and required negative pregnancy tests before a drug’s distribution to avoid severe birth defects.<sup>41</sup>

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<sup>31</sup> FDA, CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION & RESEARCH, GUIDANCE FOR INDUSTRY, FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS), REMS ASSESSMENTS, AND PROPOSED REMS MODIFICATIONS 3 (2009) [hereinafter FDA, GUIDANCE FOR INDUSTRY], <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf> [https://perma.cc/6XUN-TARG].

<sup>32</sup> *Id.*

<sup>33</sup> *Id.*

<sup>34</sup> FDA, STANDARDIZING AND EVALUATING RISK EVALUATION AND MITIGATION STRATEGIES (REMS) 9 (2014) [hereinafter FDA, STANDARDIZING REMS], <https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm415751.pdf> [https://perma.cc/L83N-UN8B].

<sup>35</sup> Pub. L. No. 110-85, 121 Stat. 823 (2007) (codified as amended at 21 U.S.C. § 355-1).

<sup>36</sup> The requirements apply to brand firms filing NDAs, generics filing ANDAs, and biologic manufacturers filing biologics license applications (“BLAs”). FDA, STANDARDIZING REMS, *supra* note 34, at 9.

<sup>37</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 505-1(a)(1), 121 Stat. 823, 926 (codified as amended at 21 U.S.C. § 355-1(a)(1)).

<sup>38</sup> FDA, GUIDANCE FOR INDUSTRY, *supra* note 31, at 5.

<sup>39</sup> *Id.*

<sup>40</sup> FDA, A BRIEF OVERVIEW OF RISK EVALUATION & MITIGATION STRATEGIES (REMS) 2 [hereinafter FDA, BRIEF OVERVIEW], <http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf> [https://perma.cc/8MFG-CE8F] (last visited Sept. 17, 2017).

<sup>41</sup> *Id.* at 3, 13, 19.

In determining the need for REMS, the FDA considers six factors: (1) the population size likely to use the drug, (2) the seriousness of the disease, (3) the drug's expected benefit, (4) the expected duration of treatment, (5) the seriousness of adverse effects, and (6) the drug's novelty.<sup>42</sup> The FDA can require a REMS before a drug enters the market based on known risks or after the drug has been approved based on new evidence of risk.<sup>43</sup>

All REMS must include a timetable for submission of periodic reports to the FDA regarding the REMS program.<sup>44</sup> Other requirements vary depending on the risk profile of the drug and the need to inform doctors or patients of safety concerns.<sup>45</sup> REMS programs differ in their level of restriction. The "least restrictive" programs may include medication guides for patients and communication plans for healthcare practitioners.<sup>46</sup>

More restrictive REMS programs have "Elements to Assure Safe Use" ("ETASU"), which can include prescriber experience requirements, certification systems, patient monitoring or registration, and controlled distribution.<sup>47</sup> These requirements restrict a drug's distribution and affect how it can be sold to consumers. ETASU measures are "designed to be compatible with established distribution, procurement, and dispensing systems for drugs."<sup>48</sup>

REMS programs can be required for a single drug or an entire class of drugs.<sup>49</sup> The opioid REMS program, for example, involves multiple companies,<sup>50</sup> making the fight against the public health problem of opioid abuse a more coordinated effort. The shared REMS program has resulted in more prescribers receiving training on pain management and on the safe prescription of opioids.<sup>51</sup>

<sup>42</sup> *Id.* at 6.

<sup>43</sup> 21 U.S.C.A. § 355-1(a)(1), (a)(2)(A) (West 2017).

<sup>44</sup> Unlike brand drugs, generics are not required to independently submit a timetable for periodic FDA assessments. *See* FDA, STANDARDIZING REMS, *supra* note 34, at 15; *see also* FDA, BRIEF OVERVIEW, *supra* note 40, at 17 (stating that FDA assessments under a timetable "must be [conducted] at least by 18 months, 3 years, and in the 7th year after the REMS is approved" and "[c]an be eliminated after 3 years").

<sup>45</sup> Shashank Upadhye & Braden Lang, *The FDA and Patent, Antitrust, and Property Takings Laws: Strange Bedfellows Useful to Unblock Access to Blocked Drugs*, 20 B.U. J. SCI. & TECH. L. 84, 92-95 (2014).

<sup>46</sup> *Id.* at 93.

<sup>47</sup> FDA, BRIEF OVERVIEW, *supra* note 40, at 13; Upadhye & Lang, *supra* note 45, at 94.

<sup>48</sup> 21 U.S.C.A. § 355-1(f)(2)(D)(ii).

<sup>49</sup> FDA, BRIEF OVERVIEW, *supra* note 40, at 4.

<sup>50</sup> FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)* [hereinafter FDA, *Approved REMS*], <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=17> [<https://perma.cc/D76T-QGMH>] (last visited Sept. 17, 2017) (listing 19 branded compounds and 40 generic compounds covered by opioid REMS program).

<sup>51</sup> FDA, *Fact Sheet—FDA Opioids Action Plan* <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm> [<https://perma.cc/B7D9-7C64>] (last visited June 23, 2017); *see also* FDA, *Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release*

Since their initiation in 2007, REMS programs—in particular those with ETASU requirements—have become an increasingly prominent part of the FDA approval process. Almost 40% of new drugs have REMS programs.<sup>52</sup> There are currently 70 approved and active REMS programs, 33 of which require ETASU measures.<sup>53</sup> The prevalence of ETASU requirements marks a shift from early REMS programs, which tended to call only for the less restrictive requirement of medication guides.<sup>54</sup> Despite their increasing frequency, a report by the U.S. Department of Health and Human Services’ Office of Inspector General questioned “the overall effectiveness of the REMS program,” with just 7 of 49 REMS meeting all of their goals.<sup>55</sup> As technology and individualized medicine play a larger role in health care, REMS programs will become even more significant.<sup>56</sup> And as the programs increase, REMS patents could become more prevalent.

### C. *REMS Patents*

REMS patents threaten generic competition, a fundamental principle underlying the Hatch-Waxman Act, state DPS laws, and the FDEAA.

For starters, the Hatch-Waxman Act allows for “piggy-back[ing]”<sup>57</sup> by generics, experimentation during the patent term, and 180-day marketing exclusivity—all provisions that promote generic competition.<sup>58</sup> To foster this competition, the generic must show that its drug is bioequivalent—in other

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*and Long-Acting Opioid Analgesics* (Jan. 9, 2017), <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm> [<https://perma.cc/7ECT-MD3K>] (stating that REMS is “one strategy among multiple national and state efforts to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics”).

<sup>52</sup> ALEX BRILL, MATRIX GLOB. ADVISORS, LOST PRESCRIPTION DRUG SAVINGS FROM USE OF REMS PROGRAMS TO DELAY GENERIC MARKET ENTRY 2 (2014), [http://www.gphaonline.org/media/cms/REMS\\_Studyfinal\\_July2014.pdf](http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf) [<https://perma.cc/F69B-WS5P>].

<sup>53</sup> FDA, *Approved REMS*, *supra* note 50 (follow “Data Files” hyperlink; then follow “Download REMS Versions Data (REMS\_Versions.csv)” hyperlink).

<sup>54</sup> BRILL, *supra* note 52, at 3.

<sup>55</sup> DEP’T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECTOR GEN., FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY 16, 22 (2013), <https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf> [<https://perma.cc/64Z6-MKP2>].

<sup>56</sup> Stephen B. Maebius et al., *Patenting Risk Evaluation & Mitigation Strategies for Pharmaceuticals: A New Life Cycle Management Target for Patents?*, 7 PHARMACEUTICAL L. & INDUSTRY REP. 1, 3 (2009) (“As genomic information, biomarker assays, and other types of clinical data collected from clinical trials continue to yield new insights into the mechanisms responsible for drug efficacy as well as drug side effects, the universe of potentially patentable risk mitigation strategies will continue to grow.”).

<sup>57</sup> Fed. Trade Comm’n v. Actavis, Inc., 133 S. Ct. 2223, 2228 (2013).

<sup>58</sup> See *supra* notes 18-23 and accompanying text; see also Carrier, *supra* note 12, at 41-47 (detailing mechanisms adopted to promote generic competition).



words, that the rate and extent of absorption in the body is roughly equivalent to that of the brand drug.<sup>59</sup>

When a brand company's drug is subject to a REMS program, the generic must implement an identical program. The FDA has made this clear: "If we are approving a generic drug and there is a REMS in place for the innovator drug, the requirements are the same for the ANDA product."<sup>60</sup> The agency also has confirmed that if generics and brands cannot successfully negotiate shared REMS, then the programs will be "equal."<sup>61</sup>

REMS patents raise infringement concerns in the context of not only separate but also shared programs. Under the REMS statute, when a company seeks approval for a generic version of a branded drug containing a REMS with ETASU program, the generic and brand must work together to create a Single Shared REMS program ("SSRS").<sup>62</sup> The FDA may waive this shared-system requirement and allow a generic to file its own REMS in two situations.<sup>63</sup> The first applies when the burden of creating a single system outweighs the benefits.<sup>64</sup> The second happens when an aspect of the ETASU is "claimed by a patent that has not expired or is a method or process that, as a trade secret, is entitled to protection"<sup>65</sup> and the generic certifies that it has taken (unsuccessful) steps to obtain a license.<sup>66</sup>

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<sup>59</sup> See generally FDA, CTR. FOR DRUG EVALUATION AND RESEARCH, *Orange Book Preface* (Jan. 24, 2017), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm> [<https://perma.cc/R36V-P6YH>] (defining "bioequivalent drug products" and outlining the Orange Book's history and function).

<sup>60</sup> *FDA Basics Webinar: A Brief Overview of Risk Evaluation & Mitigation Strategies (REMS)*, FDA, <https://collaboration.fda.gov/p97727926/?launcher=false&fcsContent=true&pbMode=normal> [<https://perma.cc/3U46-UFUX>] (last visited Sept. 17, 2017).

<sup>61</sup> STAFF OF S. COMM. ON AGING, 114TH CONG., REP. ON SUDDEN PRICE SPIKES IN OFF-PATENT PRESCRIPTION DRUGS: THE MONOPOLY BUSINESS MODEL THAT HARMS PATIENTS, TAXPAYERS, AND THE U.S. HEALTH CARE SYSTEM 116 (2016) (quoting Dr. Janet Woodcock, Director, FDA, Center for Drug Evaluation and Research); see Elaine Lippmann, FDA, *Development of Single, Shared System REMS*, in GPHA FALL TECHNICAL CONFERENCE 17 (2016), [http://www.gphaonline.org/media/wysiwyg/Meetings/Fall\\_2016/Elaine\\_Lippmann.pdf](http://www.gphaonline.org/media/wysiwyg/Meetings/Fall_2016/Elaine_Lippmann.pdf) [<https://perma.cc/M7WJ-6MBZ>] (declaring that REMS for ANDAs have the "[s]ame goals" and "[s]ame ETASU," which "[c]ontain the same elements" and "[m]ust achieve [the] same level of safety"); Letter from Janet Woodcock, Director, FDA, Center for Drug Evaluation & Research, to William Franzblau, Vice President, Prometheus Labs., Inc., Docket No. FDA-2013-P-0572, at 6 (Oct. 7, 2013) (stating that brand and generic firms participating in SSRS "have been subject to the same ETASU, implementation system, and assessments").

<sup>62</sup> 21 U.S.C.A. § 355-1(i)(1)(B) (West 2017).

<sup>63</sup> *Id.*

<sup>64</sup> *Id.* § 355-1(i)(1)(B)(i).

<sup>65</sup> *Id.* § 355-1(i)(1)(B)(ii).

<sup>66</sup> *Id.* To obtain this type of waiver, the generic's certification to the FDA must include a description of the efforts taken to obtain a license. *Id.*

Even though the FDA has the authority to waive a brand's obligation to share its REMS program, that does not address the infringement concerns implicated by REMS patents. An FDA waiver does not determine the claim scope of a REMS patent, nor does the agency play any role in determining the extent of infringement liability. Even if the FDA grants a waiver from the SSRS and the generic obtains approval of its own REMS, a generic is not likely to avoid infringement where the brand has patented its REMS program.<sup>67</sup>

It should not be a surprise, then, that brands have contended that generics cannot create their own REMS programs without committing patent infringement. One example was provided by Celgene's citizen petition regarding its patented REMS program for Thalomid, a drug originally used as a sleeping pill to treat morning sickness during pregnancy (but notoriously linked to severe birth defects and fetal deaths).<sup>68</sup> When Barr Laboratories sought approval for a generic version of Thalomid, Celgene filed a petition in which it contended that it "firmly believes that its patents directed to [its REMS] program preclude Barr's proposed plan."<sup>69</sup> Celgene also questioned the FDA's authority to share patented material, asserting that the agency "has [n]either the authority [n]or the right to expect Celgene to share its patented technology or business methods with a company that seeks to directly compete with one of Celgene's primary products."<sup>70</sup>

In addition to triggering infringement claims, REMS patents undermine crucial FDAAA policies. Congress included a provision in the statute that made clear that ETASU measures could not be used to prevent generic firms from accessing samples of drugs covered by REMS.<sup>71</sup> In particular, the statute explicitly states that "[n]o holder of an approved covered application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application."<sup>72</sup> Such language provides not only

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<sup>67</sup> See Maximilian A. Grant et al., *Not Yet: Patented Risk Evaluation and Mitigation Strategies May Delay (or Tax) Competitors*, INTELL. PROP. TODAY, June 2009, at 12 (demonstrating that the equivalency standard against which a generic is tested will require it to propose near identical REMS measures, thereby committing infringement of the brand's patent). A generic could conceivably avoid infringement if the patent has a narrow claim scope that does not cover the REMS program, but we do not anticipate that this will happen because a brand is not likely to obtain and list a REMS patent that does not claim the REMS program listed in the label.

<sup>68</sup> See Complaint at 1, *Lannett Co. v. Celgene Corp.*, No. 2:08-cv-03920 (E.D. Pa. filed Aug. 15, 2008), 2011 WL 1193912.

<sup>69</sup> Petition of Celgene Corp. at 23, No. FDA-2007-P-0113-0002 (Sept. 20, 2007), available at <http://www.regulations.gov>.

<sup>70</sup> *Id.*

<sup>71</sup> See 21 U.S.C.A. § 355-1(f)(8).

<sup>72</sup> *Id.* (emphasis added). The full text reads:

No holder of an approved covered application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application under [21 U.S.C. §] 355(b)(2) or (j) . . . or to prevent application of such

that brands shall not use REMS to *block* generics but also that they shall not use them to *delay* generics. The FDAAA also provided that REMS programs would not burden the healthcare system, particularly for patients who “have difficulty accessing health care (such as patients in rural or medically underserved areas)” or those with “serious or life-threatening diseases or conditions.”<sup>73</sup> In enacting the FDAAA, Congress did not intend for REMS programs to block generic competition.

## II. THE PATENT PROBLEM

Generics confront significant challenges due to the patenting of REMS programs. This Part first raises concerns presented by improper patent listings in the Orange Book and then discusses generic infringement of REMS patents.

### A. Orange Book Listings

The Hatch-Waxman Act instituted a carefully choreographed system by which brands and generics would litigate patents. In recent years, this process has increasingly applied to REMS patents.

Hatch-Waxman litigation, by which a brand sues a generic for patent infringement, is based on the Orange Book, an annual publication (updated daily on the FDA’s website) that offers a centralized listing of drugs and their associated patents.<sup>74</sup> Upon filing an NDA, a brand firm lists any relevant patents in the Orange Book.<sup>75</sup> The generic company then typically files its application, making one of four possible certifications for each of the brand’s listed patents.<sup>76</sup> The certification that most directly implicates competition, the “paragraph IV” certification, is based on the generic’s assertion that the brand’s patent is invalid or will not be infringed.<sup>77</sup> Filing a paragraph IV certification is treated as an act of artificial infringement, allowing the brand to immediately file a lawsuit.<sup>78</sup> Raising the significance of Orange Book listings, such a lawsuit provides the brand with an automatic stay that prevents the FDA from approving the generic for 30 months.<sup>79</sup>

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element under [21 U.S.C. § 355-1(i)(1)(B)] to a drug that is the subject of an abbreviated new drug application.

*Id.*

<sup>73</sup> *Id.* § 355-1(f)(2)(C).

<sup>74</sup> See FDA, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (May 2017), <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm> [<https://perma.cc/9Z9F-ASY5>].

<sup>75</sup> See 21 U.S.C.A. § 355(b)(1).

<sup>76</sup> See *id.* § 355(j)(2)(A)(vii).

<sup>77</sup> See *id.* § 355(j)(2)(A)(vii)(IV).

<sup>78</sup> 35 U.S.C. § 271(e)(2) (2012).

<sup>79</sup> 21 U.S.C.A. § 355(j)(5)(B)(iii). For a discussion of how the stay can be extended or shortened, see SHASHANK UPADHYE, *GENERIC PHARMACEUTICAL PATENT AND FDA LAW* § 11:13, Westlaw (database updated July 2016).

A limited subset of patents can be listed in the Orange Book and trigger the 30-month stay.<sup>80</sup> The Hatch-Waxman Act makes clear that the only patents that can be listed are those that claim the “drug” or “method of using such drug.”<sup>81</sup> The FDA’s interpretation of this category includes patents claiming an active ingredient, formulation, composition, product-by-process, and method of approved use, but does not cover processes, packaging, metabolites, or intermediates.<sup>82</sup> The Orange-Book concern with REMS patents is that they do not claim “the drug” or “a method of using” the drug<sup>83</sup> but instead claim a method or system of mitigating a drug’s risks by monitoring a product’s distribution. Stated differently, a REMS patent claims not a drug’s *use* but a method of *complying* with an FDA-imposed requirement.<sup>84</sup>

We reviewed the 2017 edition of the Orange Book and determined that the following five drug products with REMS programs have listed patents claiming aspects of the programs<sup>85</sup>: Entereg, Xyrem, and three of Celgene’s thalidomide-

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<sup>80</sup> See UPADHYE, *supra* note 79, § 6:9. For an in-depth discussion of Orange Book listability, see *id.* § 6.

<sup>81</sup> 21 U.S.C.A. § 355(b)(1)(G).

<sup>82</sup> 21 C.F.R. § 314.53(b)(1) (2017); see UPADHYE, *supra* note 79, § 6:10 (summarizing listable and nonlistable patents); see, e.g., *Cadence Pharm., Inc. v. Fresenius Kabi USA, LLC*, No. 13-0139, 2014 WL 12139078, at \*2 (S.D. Cal. June 5, 2014) (“Potential for abuse arises when an NDA applicant or holder characterizes a patent as a product-by-process patent and submits it for listing in the Orange Book, when in fact the patent is a process patent which must not be listed.”).

<sup>83</sup> 21 U.S.C.A. § 355(b)(1)(G).

<sup>84</sup> We focus in this Article on REMS patents listed for small-molecule drugs in the Orange Book. Such an emphasis does not address every conceivable REMS patent. Brand firms, for example, may hold the rights to REMS patents that they have not yet listed in the Orange Book. We also do not address the role played by REMS patents in the biologics market, which is governed by the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”), Pub. L. No. 111-148, 124 Stat. 804. As of June 23, 2017, the FDA had required REMS with ETASU for 12 biologic compounds: Aransep, Epogen/Procrit, Lemtrada, Lumizyme, Myalet, Natapra, Nplate, Siliq, Soliris, Tysabri, Xiaflex, and Zinbryta. See FDA, *Approved REMS*, *supra* note 50 (follow “Data Files” hyperlink; follow “Download REMS Drugs Data (REMS\_Products.csv)” and “Download REMS Versions Data (REMS\_Versions.csv)” hyperlinks). Under the BPCIA, biologic manufacturers are not required to list patents in a centralized publication like the Orange Book. Instead, relevant patents to be litigated are identified through a complex negotiation process known as the “patent dance.” See 42 U.S.C. § 262(l) (2012); see generally *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664 (2017) (interpreting biosimilar framework to allow earlier follow-on marketing than the Federal Circuit had allowed). The absence of an Orange Book for biologics precludes the use of a 30-month stay.

<sup>85</sup> We located REMS patents in the Orange Book in several steps. First, on April 4, 2017, we downloaded the FDA’s list of drugs required to carry REMS programs, available on the FDA’s website: <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>. This list includes the product name, whether the product is subject to a shared system, the date each program was last updated, the date the REMS program was first approved, the application number for each product subject to the REMS program, and whether the REMS product

derived<sup>86</sup> products—Pomalyst, Revlimid, and Thalomid (which we collectively refer to as the “Celgene drugs”). For these five drugs, there were 83 separate patent listings, with more than half (43) consisting of REMS patents.<sup>87</sup> Given the variety of patents that can be listed for a given product, it is concerning that 52% of the listings addressed a type that by all reasonable accounts is unlistable. As seen in Table 1, 10 of the REMS patents are owned by Celgene and have been listed 3 times for each of the Celgene drugs.<sup>88</sup> In other words, the 43 listings apply to 23 distinct patents.

**Table 1.** REMS Patents Listed in Orange Book, by U.S. Patent Number

Entereg	Pomalyst	Revlimid	Thalomid	Xyrem
8,112,290	6,045,501	6,045,501	6,045,501	7,668,730
8,645,160	6,315,720	6,315,720	6,315,720	7,765,106
	6,561,976	6,561,976	6,561,976	7,765,107
	6,561,977	6,561,977	6,561,977	7,895,059
	6,755,784	6,755,784	6,755,784	8,457,988
	6,908,432	6,908,432	6,908,432	8,589,182

involved a medication guide, communication plan, ETASU, and/or implementation system. We then researched patents listed in the Orange Book for each application number included in the FDA’s REMS document. Finally, we identified REMS patents by reading the title, abstract, and claims for each listed patent.

<sup>86</sup> Introduced in the 1950s, thalidomide was initially abandoned for causing pregnancy complications and developmental problems. In the 1990s, however, studies began to show that thalidomide derivatives had a unique set of antitumor characteristics helpful in combating, among other diseases, multiple myeloma. See Tahir Latif et al., *Thalidomide and Its Analogues in the Treatment of Multiple Myeloma*, 1 EXPERIMENTAL HEMATOLOGY & ONCOLOGY, no. 27, 2012, at 1 (summarizing thalidomide’s initial market introduction, subsequent abandonment, and later reentry into clinical use as an oncology treatment).

<sup>87</sup> For example, in addition to the two REMS patents listed for Entereg, the drug’s sponsor, Cubist Pharmaceuticals, also lists patent numbers 6,469,030 and 8,946,262, each of which claims methods of treating or preventing gastrointestinal dysfunction. U.S. Patent No. 6,469,030 (filed Nov. 29, 2000); U.S. Patent No. 8,946,262 (filed Nov. 29, 2004). As we discuss below, listing method-of-treatment patents in the Orange Book is appropriate, while listing REMS patents is not.

<sup>88</sup> Because the Hatch-Waxman Act allows the listing of “any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug,” 21 U.S.C.A. § 355(b)(1), brands often list multiple patents in the Orange Book. *E.g.*, JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 422, Bloomberg BNA (3d ed. 2017).

**Table 1.** REMS Patents Listed in Orange Book, by U.S. Patent Number (cont'd)

Entereg	Pomalyst	Revlimid	Thalomid	Xyrem
	8,204,763	8,204,763	8,204,763	8,731,963
	8,315,886	8,315,886	8,315,886	
	8,589,188	8,589,188	8,589,188	
	8,626,531	8,626,531	8,626,531	
			6,869,399	
			7,141,018	
			7,874,984	
			7,959,566	

The two Entereg patents listed in the first column of Table 1 claim priority to an application filed in 2008 and were issued in 2012 and 2014. Titled “[m]ethods for delivering a drug to a hospital patient for short-term use while minimizing long-term use of the drug,”<sup>89</sup> these patents claim methods for identifying a hospital and registering the hospital and patients in “computer readable storage media” to ensure that Entereg is safely dispensed.<sup>90</sup>

The next group, appearing in the second, third, and fourth columns, involves the 14 patents listed for Celgene’s three thalidomide drugs. This group consists of two patent families, deriving from two original patent applications.<sup>91</sup> The first application, filed in 1998, resulted in the Elsayed Family (named after the inventor), which consists of six patents.<sup>92</sup> The second application, filed in 2000, resulted in the Williams Family (also named after the inventor), which consists

<sup>89</sup> In obtaining the benefit of an earlier filing date in a parent application, and to maintain continuity of disclosure, an invention’s title is usually the same for all patents in the family. *See* 35 U.S.C. § 120 (2012).

<sup>90</sup> U.S. Patent No. 8,645,160 (filed July 3, 2012).

<sup>91</sup> *See* 1 ROBERT A. MATTHEWS, JR., ANNOTATED PATENT DIGEST § 6:53, Westlaw (database updated June 2017).

<sup>92</sup> Titled “[m]ethods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug,” the Elsayed Family includes the following U.S. Patents: 6,045,501; 6,561,976; 6,908,432; 7,874,984; 8,204,763; and 8,589,188. *See* U.S. Patent Application No. 13/473,725 (filed May 17, 2012).

of eight patents.<sup>93</sup> In late 2015, five of the Celgene patents<sup>94</sup> (together with five other patents) were the basis of a settlement allowing the entry of a generic copy of Revlimid.<sup>95</sup>

Finally, the seven patents listed in the fifth column for narcolepsy drug Xyrem claim REMS distribution. Each of these patents derives from the same original application<sup>96</sup> and claims some version of a drug distribution system and method that utilizes a central pharmacy and database to track prescriptions for a sensitive drug.<sup>97</sup> By the spring of 2017, and as we discuss below,<sup>98</sup> all seven patents were invalidated through IPR at the PTO.<sup>99</sup> One claim from U.S. Patent No. 7,668,730 is instructive:

1) A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the [sic] any and all medical doctors;

requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are

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<sup>93</sup> Titled “[m]ethods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated,” the Williams Family includes the following U.S. Patents: 6,315,720; 6,561,977; 6,755,784; 6,869,399; 7,141,018; 7,959,566; 8,315,886; and 8,626,531. *See* U.S. Patent Application No. 13/591,622 (filed Aug. 22, 2012).

<sup>94</sup> *See* U.S. Patent Nos. 6,045,501 (filed Aug. 28, 1998); 6,315,720 (filed Oct. 23, 2000); 6,561,976 (filed Sept. 26, 2001); 6,561,977 (filed Sept. 27, 2001); and 6,755,784 (filed Mar. 7, 2003).

<sup>95</sup> Kat Greene, *Celgene Allows Earlier Cancer Drug Generic in Patent Deal*, LAW360 (Dec. 22, 2015, 11:06 PM), <https://www.law360.com/articles/741358/celgene-allows-earlier-cancer-drug-generic-in-patent-deal>.

<sup>96</sup> U.S. Patent Application No. 10/322,348 (filed Dec. 17, 2002).

<sup>97</sup> Continuation applications are derived from and filed during the pendency of an earlier application—i.e., a parent application—and claim only subject matter disclosed in the prior application. Patentees often use continuation applications to broaden their patent portfolios. *See, e.g.*, Max Colice, *Using Continuation Applications Strategically*, COOLEYGO, <https://www.cooleygo.com/using-continuation-applications-strategically/> [https://perma.cc/N6S4-GC5L] (last visited Sept. 17, 2017).

<sup>98</sup> *See infra* notes 223-33 and accompanying text.

<sup>99</sup> Matthew Bultman, *PTAB Nixes 6 Jazz Pharma Patents in AIA Review by Rivals*, LAW360 (July 28, 2016, 10:21 AM), <https://www.law360.com/articles/822645/ptab-nixes-6-jazz-pharma-patents-in-aia-reviews-by-rivals> (discussing IPR invalidation of six Xyrem patents).

processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug;

confirming with a patient that educational material has been read prior to shipping the prescription drug;

checking the exclusive computer database for potential abuse of the prescription drug;

mailing the prescription drug to the patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug;

confirming receipt by the patient of the prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.<sup>100</sup>

This claim raises significant questions of patentability and infringement that we discuss below.<sup>101</sup>

#### B. *Patent Infringement*

There are three types of patent infringement. First, direct infringement occurs when someone without authority makes, uses, offers to sell, or sells any patented invention.<sup>102</sup> In the case of method patents, direct infringement can be divided among multiple actors.<sup>103</sup> Courts “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.”<sup>104</sup>

The second and third types of infringement are indirect in nature. The second, contributory infringement, occurs when an alleged infringer sells a component of a claimed invention to another, who then directly infringes.<sup>105</sup> The third, induced infringement, requires proof that the alleged infringer knowingly aided and abetted another’s direct infringement.<sup>106</sup> Like contributory infringement, liability for induced infringement “must be predicated on direct

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<sup>100</sup> U.S. Patent No. 7,668,730 (filed Dec. 17, 2002).

<sup>101</sup> See *infra* Sections II.B, III.B.

<sup>102</sup> 35 U.S.C. § 271(a) (2012).

<sup>103</sup> *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (en banc) (per curiam) (“Where more than one actor is involved in practicing the steps, a court must determine whether the acts of one are attributable to the other such that a single entity is responsible for the infringement.”).

<sup>104</sup> *Id.*

<sup>105</sup> 35 U.S.C. § 271(c).

<sup>106</sup> *Id.* § 271(b); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003).



infringement.”<sup>107</sup> The patentee also must “show that the alleged infringer possessed the requisite intent to induce infringement,”<sup>108</sup> which requires that the alleged infringer “knew or should have known” that its actions “would induce actual infringements.”<sup>109</sup>

The Federal Circuit recently addressed induced infringement in *Eli Lilly & Co. v. Teva Parenteral Medicines*.<sup>110</sup> In that case, a brand firm marketed a chemotherapy drug and listed in the Orange Book a method-of-treatment patent that required an initial step of administering a drug to a patient.<sup>111</sup> The brand sued the generic, claiming that the proposed generic label (which provided instructions on how to administer the drug) would induce infringement of its method-of-treatment patent.<sup>112</sup> The Federal Circuit agreed, explaining that “[w]hen the alleged inducement relies on a drug label’s instructions, ‘the question is not just whether those instructions describe the infringing mode, . . . but whether the instructions teach an infringing use such that we are willing to infer from those instructions an affirmative intent to infringe the patent.’”<sup>113</sup> The court highlighted the proposed label’s inclusion of “repeated instructions and warnings regarding the importance of and reasons for” the initial step of administering the drug.<sup>114</sup>

The existence of REMS patents puts would-be generic competitors in an untenable position. When the FDA approves a brand’s REMS program, the brand will typically describe the REMS in the product’s label.<sup>115</sup> At the same time, however, a generic applicant must show that its proposed labeling is the same as that of the brand drug.<sup>116</sup> For that reason, the generic’s label must

<sup>107</sup> *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2117 (2014).

<sup>108</sup> *Eli Lilly & Co. v. Teva Parenteral Meds.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017).

<sup>109</sup> *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1304 (Fed. Cir. 2006) (en banc in relevant part).

<sup>110</sup> *Eli Lilly*, 845 F.3d at 1363; *see also* *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm., Corp.*, 785 F.3d 625, 628 (Fed. Cir. 2015).

<sup>111</sup> *Eli Lilly*, 845 F.3d at 1361-63.

<sup>112</sup> *Id.*

<sup>113</sup> *Id.* at 1368 (alterations and emphasis omitted) (quoting *Takeda*, 785 F.3d at 631).

<sup>114</sup> *Id.* at 1369.

<sup>115</sup> 21 U.S.C.A. § 355-1(e)(2) (West 2017) (“The risk evaluation and mitigation strategy for a drug may require that, as applicable, the responsible person develop for distribution to each patient when the drug is dispensed . . . a patient package insert, if the Secretary determines that such insert may help mitigate a serious risk of the drug.”). In the case of Entereg, for example, the package insert describes all the steps associated with the ENTEREG Access Support and Education (E.A.S.E.) REMS Program. *See* Merck & Co., Inc., Entereg Label § 5.2 (2008), [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/021775s010lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021775s010lbl.pdf) [<https://perma.cc/K8DZ-FMDQ>].

<sup>116</sup> 21 U.S.C.A. § 355(j)(4)(G) (“[L]abeling proposed for the [generic] is the same as the labeling approved for the listed drug.”).

include the REMS program that appears in the brand's label.<sup>117</sup> If the brand has a patent on its REMS program, then the generic finds itself in a catch-22 situation: either (1) include the REMS program in its package insert and potentially infringe or (2) do not include the program and violate the FDA's package insert laws.

One vivid example of how the language of a REMS program described in a brand's label can overlap with a REMS patent appears in the case of Entereg. The Entereg '160 patent claims a method of treating a patient undergoing abdominal surgery by administering a 12-mg dose of Entereg less than one day before surgery and then twice daily after surgery. Table 2 below reveals how the REMS program language that must be included in the Entereg label is virtually identical to that of the '160 patent.

**Table 2.** Entereg '160 Patent and REMS Program

U.S. Patent No. 8,645,160, Claim 1	Entereg REMS Program
A method of treating a subject undergoing abdominal surgery comprising orally administering to the subject a composition comprising about 12 mg of [Entereg] less than one day prior to surgery followed by administering [Entereg] to the subject twice daily beginning the day after surgery,	—
wherein the method is carried out in a hospital that has acknowledged that:	To enroll in the E.A.S.E. Program, an authorized hospital representative must acknowledge that:
(i) hospital staff who prescribe, dispense or administer [Entereg] have been provided education materials on the need to limit the use of [Entereg] to short-term, inpatient use;	hospital staff who prescribe, dispense, or administer ENTEREG have been provided the educational materials on the need to limit use of ENTEREG to short-term, inpatient use;
(ii) the subject will not receive more than 15 total doses of [Entereg]; and	patients will not receive more than 15 doses of ENTEREG; and
(iii) [Entereg] will not be dispensed to the subject after being discharged from the hospital.	ENTEREG will not be dispensed to patients after they have been discharged from the hospital.

<sup>117</sup> *Id.* § 355-1(i)(1) (“A drug that is the subject of an abbreviated new drug application . . . is subject to . . . the following elements of the risk evaluation and mitigation strategy required under subsection (a) for the applicable listed drug: . . . [a] Medication Guide or patient package insert, if required under subsection (e) for the applicable listed drug.”).

It is hard to see how the generic's inclusion of the brand's REMS program in the label would not lead to a claim of induced infringement.<sup>118</sup> As in the method-of-treatment context, where a generic's label tells a provider how to administer a drug (causing the provider to directly infringe based on the generic label's inducement),<sup>119</sup> so too would a generic induce providers to directly infringe a REMS patent by describing the steps of a claimed REMS program. In fact, a generic's labeling would manifest a "specific intent and action to induce infringement."<sup>120</sup> As the Federal Circuit noted in *Eli Lilly*: "the requisite intent for inducement" is established by "evidence that the product labeling that [the generics] seek would inevitably lead some physicians to infringe."<sup>121</sup>

Additional evidence of a "specific intent to induce infringement" could be revealed by the "decision to continue seeking FDA approval of . . . instructions."<sup>122</sup> Even if some users do not follow the instructions or there are substantial noninfringing uses, the Federal Circuit has held that a label "instruct[ing] users to follow the instructions in an infringing manner [is] sufficient" evidence of intent to induce infringement.<sup>123</sup> Patented REMS instructions do not offer even these possibilities as they are not likely to reveal substantial noninfringing uses given the limited purpose of a REMS program and are not likely to be vague enough that one would need to "look outside the label to understand the alleged implicit encouragement."<sup>124</sup> In fact, the *point* of REMS labeling programs is to centralize the relevant information in order to

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<sup>118</sup> 1 PATENT OFFICE LITIGATION § 21:21, Westlaw (database updated Jan. 2017) (explaining that REMS patents present concern because generic applicants "cannot use the same drug labeling as the [brand] without infringing the ETASU patent absent a discretionary waiver from the FDA").

<sup>119</sup> In the case of REMS patents, direct infringement would occur as healthcare providers follow the claimed distribution method—for example, registering with a pharmacy. Some REMS patents could result in divided infringement, in which patients, doctors, and pharmacists each perform different steps of the claimed method. In these situations, the *Akamai* case would hold an entity responsible for others' performance of method steps in two settings: where that entity directs or controls others' performance or where the actors form a joint enterprise. *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (en banc) (per curiam). Direct infringement liability "can also be found when an alleged infringer [1] conditions participation in an activity or receipt of a benefit upon performance of a step or steps of a patented method and [2] establishes the manner or timing of that performance." *Id.* at 1023.

<sup>120</sup> *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015).

<sup>121</sup> *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017).

<sup>122</sup> *Eli Lilly*, 845 F.3d at 1368; *see also* *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1059 (Fed. Cir. 2010) (finding that specific intent could be based on "decision to proceed with . . . planned distribution of the generic drug and the affirmative evidence of intent provided by the proposed label").

<sup>123</sup> *Eli Lilly*, 845 F.3d at 1368-69.

<sup>124</sup> *Id.* at 1369.

standardize the distribution of a potentially harmful drug, thereby reducing the chances of dangerous uses. In short, the generic likely will induce infringement.

Given the interplay between REMS programs and product labeling, REMS patents pose significant induced infringement concerns for generics. The purpose of REMS programs is to mitigate risk. And that risk is reduced by describing REMS programs in product literature<sup>125</sup> that must be followed by downstream users, namely pharmacists, physicians, and patients. Induced infringement is unavoidable because the very nature of REMS programs requires generics to adopt a program equal to the brand's, and FDA regulations require generics to copy brand labels.<sup>126</sup>

As a result, generics seeking to introduce REMS programs are stuck between the rock of FDA regulations and hard place of patent law. Given the safety concerns justifying identical labels, the FDA rock is immovable, with generics having no leeway to make alterations. For that reason, the next Part offers solutions to address the hard place of patent law.

### III. POTENTIAL SOLUTIONS

The previous Part demonstrated the risk of infringement liability that generics confront from REMS patents. This Part offers five potential solutions. First, REMS patents should be delisted from the Orange Book to avoid unwarranted 30-month stays of generic approval. Second, we propose more rigorous scrutiny of the patentability of REMS programs. Third, assuming the existence of valid and infringed REMS patents, we apply the framework the Supreme Court articulated in *eBay Inc. v. MercExchange, L.L.C.*,<sup>127</sup> concluding that damages are a more appropriate remedy than injunctions.<sup>128</sup> Fourth, we consider the policies underlying the pharmaceutical regulatory framework to recommend statutory changes that would mitigate the effect of REMS patents. Finally, like the treatment of tax-strategy patents in the AIA, we recommend that Congress deem REMS patents to fall within the prior art.

#### A. *Delisting*

To date, there have been three cases brought under the Hatch-Waxman Act<sup>129</sup> that have involved REMS patents: Xyrem, Revlimid, and Thalomid.<sup>130</sup> In all

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<sup>125</sup> Product literature can include, among other elements, labeling, communication plans, and medication guides.

<sup>126</sup> See *supra* notes 61-64, 112-14 and accompanying text.

<sup>127</sup> 547 U.S. 388 (2006).

<sup>128</sup> *Id.* at 394.

<sup>129</sup> Because current practice is to list REMS patents in the Orange Book, infringement actions based on these patents have been filed under 35 U.S.C. § 271(e), the statute governing infringement under the Hatch-Waxman Act.

<sup>130</sup> See generally Complaint, Celgene Corp. v. Lannett Holdings, Inc., No. 15-0697 (D.N.J. filed Jan. 30, 2015), ECF No. 1 (litigating REMS patents listed for Thalomid); Complaint,

three cases, the brand firm asserted Orange-Book-listed REMS patents along with other non-REMS patents.<sup>131</sup> In *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*,<sup>132</sup> for example, Jazz sued for infringement based on formulation patents<sup>133</sup> and REMS patents related to Xyrem, with Roxane filing a counterclaim that Jazz improperly listed the '730, '106, and '107 REMS patents.<sup>134</sup> Each of these patents referred to a “drug distribution system and method [that] utilizes a central pharmacy and database to track all prescriptions for a sensitive drug.”<sup>135</sup> Citing the FDAAA, Roxanne argued that the patents “improperly serv[ed] to block or delay approval of Roxane’s ANDA.”<sup>136</sup> Roxanne also contended that the patents should be delisted because they did not claim an approved method of using Xyrem.<sup>137</sup>

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*Jazz Pharm., Inc. v. Par Pharm., Inc.*, No. 13-7884 (D.N.J. filed Dec. 27, 2013), ECF No. 1 (litigating REMS patents listed for Xyrem); *Complaint, Celgene Corp. v. Natco Pharma Ltd.*, No. 12-4571 (D.N.J. filed July 20, 2012), ECF No. 1 (litigating REMS patents listed for Revlimid).

<sup>131</sup> *E.g.*, *Complaint at 1-2, Celgene Corp. v. Natco Pharm. Ltd.*, No. 10-5197 (D.N.J. filed Oct. 8, 2010), ECF No. 1 (asserting five Celgene REMS patents along with, among others, U.S. Patent No. 7,119,106, claiming a pharmaceutical composition, as well as U.S. Patent No. 5,635,517, claiming a method of reducing the protein tumor necrosis factor (“TNF”) alpha).

<sup>132</sup> *Roxane Labs., Inc.’s Answer, Affirmative Defenses, and Counterclaims to Plaintiff’s Complaint at 11, Jazz Pharm., Inc. v. Roxane Labs., Inc.*, C.A. No. 10-6108 (D.N.J. filed Dec. 29, 2010), ECF No. 10 [hereinafter *Roxane Labs.’ Answer*] (listing counterclaims regarding Jazz’s REMS program).

<sup>133</sup> *See Complaint at 3, Jazz Pharm., Inc. v. Roxane Labs., Inc.*, No. 10-6108 (D.N.J. filed Nov. 22, 2010), ECF No. 1 (listing patents-in-suit). The formulation patents in the case were the '889 patent, entitled “Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy,” and the '219 patent, entitled “Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy.” *Id.* By way of background, patents on drugs have covered not just the active ingredient, which is the “foundation” of a drug, but “formulat[ions] into a dosage form suitable for delivery to a patient,” such as intravenous or oral administrations. David K. Barr et al., *Types of Biological and Pharmaceutical Patents*, in *PHARMACEUTICAL AND BIOTECH PATENT LAW* § 7.3, Bloomberg BNA (David K. Barr & Daniel L. Reisner eds., 2016).

<sup>134</sup> *Roxane Labs.’ Answer, supra* note 132, at 11 (alleging that Jazz Pharmaceuticals improperly listed the '730, '106, and '107 patents). Lupin also challenged Jazz’s REMS patents as invalid. *Lupin Ltd.’s and Lupin Pharm., Inc.’s Answer, Defenses, and Counterclaims to Complaint for Patent Infringement at 46-49, Jazz Pharm. v. Lupin Ltd.*, No. 15-6548 (D.N.J. filed Dec. 14, 2015), ECF No. 11.

<sup>135</sup> *Roxane Labs.’ Answer, supra* note 132, at 11.

<sup>136</sup> *Id.*

<sup>137</sup> *Id.* at 14 (“Roxane is entitled to an Order requiring Plaintiff to correct the patent information submitted by Plaintiff for the '106 patent on the ground that the patent does not claim the approved method of using sodium oxybate.”). Roxane made the same request for

The presence of REMS patents in the Orange Book raises the issue of a brand obtaining a 30-month stay based on paragraph IV litigation when the only listed patents are REMS patents. As discussed above,<sup>138</sup> Orange Book listings are limited to “any patent which claims the *drug* for which the applicant submitted the application or which claims a *method of using such drug* with respect to which a claim of patent infringement could reasonably be asserted.”<sup>139</sup> In 2003, the FDA implemented rules governing generic applications and Orange Book listings.<sup>140</sup> The agency explained that patents on drug substances, drug products, and method-of-use patents can be listed in the Orange Book but that “[p]rocess patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates” cannot.<sup>141</sup> Demonstrating why they should not be listed, REMS patents do not claim a method of *using* a drug product for therapeutic reasons but instead claim a method of controlling a drug’s distribution through multiple layers of the supply chain—i.e., from doctors to pharmacies to patients.

Nor will generics seeking to obtain approval before a REMS patent associated with the drug expires be likely to pursue the usual methods of avoiding the patent. For example, a generic typically could (1) seek approval for an alternative use other than the use listed in the brand’s patent<sup>142</sup> or (2) claim that its product would not infringe.<sup>143</sup> These options, however, are not likely to be available for REMS patents, which (1) do not relate to a use of the drug (such as treating a specific condition) because REMS patents cover methods of delivery and distribution while preventing risk<sup>144</sup> and (2) are not likely to support a lack of infringement given the FDA’s requirement that the programs be the same.<sup>145</sup>

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the ’107 and ’730 patents. *Id.* at 14-15. No published opinions have addressed the delisting requests.

<sup>138</sup> See *supra* notes 82-84 and accompanying text.

<sup>139</sup> 21 U.S.C.A. § 355(b)(1) (West 2017) (emphasis added).

<sup>140</sup> Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays, 68 Fed. Reg. 36,676, 36,676 (June 18, 2003) (codified at 21 C.F.R. pt. 314).

<sup>141</sup> 21 C.F.R. § 314.53(b)(1) (2017). “Metabolites are the products of enzyme-catalyzed reactions that occur naturally within cells.” Edward D. Harris, *Biochemical Facts Behind the Definition and Properties of Metabolites*, [https://www.fda.gov/ohrms/dockets/ac/03/briefing/3942b1\\_08\\_Harris%20Paper.pdf](https://www.fda.gov/ohrms/dockets/ac/03/briefing/3942b1_08_Harris%20Paper.pdf) [<https://perma.cc/8EAN-ZFQZ>] (last visited Sept. 17, 2017). A chemical intermediate is “any chemical substance produced during the conversion of some reactant to a product.” *Chemical Intermediate*, ENCYCLOPEDIA BRITANNICA, <https://www.britannica.com/science/chemical-intermediate> [<https://perma.cc/N2RG-XSSX>] (last visited Sept. 17, 2017).

<sup>142</sup> Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 566 U.S. 399, 408-10 (2012).

<sup>143</sup> *Id.*

<sup>144</sup> See *supra* Section II.A.

<sup>145</sup> STAFF OF S. COMM. ON AGING, *supra* note 61, at 115-16 (quoting Dr. Janet Woodcock, Director, FDA Center for Drug Evaluation and Research) (stating that if brand and generic do not enter into shared REMS system, FDA “[let[s] the generics have their own system that is separate but equal”); *FDA Basics Webinar*, *supra* note 60 (“If we are approving a generic

Adding insult to injury, if a generic believes a patent has been improperly listed, it cannot obtain relief at the FDA, which does not evaluate delisting requests. Even if the generic submits a letter, the agency will not take any action unless “the application holder withdraws or amends its patent information in response to FDA’s request.”<sup>146</sup> In other words, the FDA will not act unless the brand *voluntarily* removes its listing from the Orange Book. The agency, in fact, does not even review the patents, believing that this is outside the scope of its expertise.<sup>147</sup>

In contrast to the inability to act at the FDA, generic applicants are able to use a private right of action to seek Orange Book delisting.<sup>148</sup> After a brand sues a generic for patent infringement, the generic can assert a counterclaim to require the brand to correct or delete the patent information on the ground that the patent does not claim the drug for which the application was approved or an approved method of using the drug.<sup>149</sup>

In facilitating the approval of noninfringing generics, courts have recognized the importance of delisting.<sup>150</sup> In *Caraco Pharmaceuticals, Ltd. v. Novo Nordisk A/S*, a brand firm obtained a patent on using repaglinide<sup>151</sup> in combination with metformin<sup>152</sup> to treat diabetes.<sup>153</sup> The FDA had approved three uses for repaglinide: (1) in combination with metformin, (2) by itself, and (3) in combination with thiazolidinediones.<sup>154</sup> Novo rewrote its use code (the listing

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drug and there is a REMS in place for the innovator drug, the requirements are the same for the [generic] product.”).

<sup>146</sup> 21 C.F.R. § 314.53(f)(i); *see* *Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1373 (Fed. Cir. 2002) (noting that FDA did not further investigate or inquire after NDA holder recertified original patent claims). *But see* Kurt R. Karst, *A New Orange Book First: FDA Unilaterally Changes a Patent Use Code*, FDA LAW BLOG (Nov. 20, 2016, 7:21 PM), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2016/11/a-new-orange-book-first-fda-unilaterally-changes-a-patent-use-code.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2016/11/a-new-orange-book-first-fda-unilaterally-changes-a-patent-use-code.html) [<https://perma.cc/3KWE-6TN4>] (describing FDA’s first unilateral change to patent use code).

<sup>147</sup> Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338-01 (Oct. 3, 1994) (to be codified at 21 C.F.R. pt. 314).

<sup>148</sup> 21 U.S.C.A. § 355(a)-(b)(1) (West 2017) (establishing procedure for applications to delist patents); *see Caraco*, 566 U.S. at 424-25.

<sup>149</sup> 21 U.S.C.A. § 355(c)(3)(D)(2)(ii)(I).

<sup>150</sup> *Caraco*, 566 U.S. at 419.

<sup>151</sup> Repaglinide is a diabetes treatment medication to lower blood glucose. *Id.* at 1679.

<sup>152</sup> Metformin is a diabetes treatment used to treat high blood sugar levels. *Drugs and Supplements Metformin (Oral Route)*, MAYO CLINIC (Mar. 1, 2017), <http://www.mayoclinic.org/drugs-supplements/metformin-oral-route/description/drg-20067074> [<https://perma.cc/8TVL-P5DL>].

<sup>153</sup> *Caraco*, 566 U.S. at 409.

<sup>154</sup> *Id.* Thiazolidinediones is a diabetes treatment medication used to reduce the body’s resistance to insulin. David Nathan, *What Are Thiazolidinediones (TZDs) and When Are They Used?*, ABC NEWS (Aug. 18, 2008), <http://abcnews.go.com/Health/DiabetesTreatment/story?id=3822110> [<https://perma.cc/4ZGC-MY5C>].

that describes the patent's scope<sup>155</sup>) in the Orange Book and claimed that its patent covered "[a] method for improving glycemic control in adults with type 2 diabetes."<sup>156</sup> Such broad language covered all three uses of repaglinide, even though Novo was only approved for repaglinide *in combination with metformin*.<sup>157</sup> The Supreme Court held that Caraco could bring an action to correct the use code because the claim was overbroad in including two uses of repaglinide for which it had not acquired a patent.<sup>158</sup>

The Court underscored the importance of delisting, explaining that a counterclaim was the only means by which Caraco could have reached the market.<sup>159</sup> Because Novo claimed all approved uses of the drug, Caraco could not seek alternative approval for a different use.<sup>160</sup> Nor could it claim that it would not infringe because of the requirement that the labeling on the drugs be identical.<sup>161</sup>

In the REMS setting, similar to overbroad Orange Book listings, listed patents describe methods of distributing a drug that prevent generic approval. Because, at a minimum, its program will be very similar, a generic most likely will not be able to prove that it will not infringe a patented REMS distribution program before approval. In fact, this setting could be even *more* problematic than the overbroad use in *Caraco* because listed REMS patents could cover much more than a drug's approved use, encompassing an entire distribution system.

We recommend that generic firms faced with 30-month stays of approval from paragraph IV litigation based on REMS-patent listings consider filing counterclaims to delist the patents. Such counterclaims would not shield the generic from litigation on the REMS patent in a separate action but would offer the chance for the generic to launch "at risk" (before a district court finds the patent invalid or not infringed)<sup>162</sup> because of the absence of a 30-month stay.<sup>163</sup>

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<sup>155</sup> FDA, *Orange Book Data Files* (Feb. 24, 2017), <https://www.fda.gov/drugs/informationondrugs/ucm129689.htm> [<https://perma.cc/5B3V-UBKR>] (defining patent use code as "[c]ode to designate use patent that covers the approved indication or use of a drug product").

<sup>156</sup> *Caraco*, 566 U.S. 399, 410 (2012).

<sup>157</sup> *Id.* at 409.

<sup>158</sup> *Id.* at 425-26.

<sup>159</sup> *Id.* at 424-25.

<sup>160</sup> *Id.*

<sup>161</sup> *Id.*

<sup>162</sup> RBC CAPITAL MKTS., PHARMACEUTICALS: ANALYZING LITIGATION SUCCESS RATES 7 (2010), <http://amlawdaily.typepad.com/pharmareport.pdf> [<https://perma.cc/M946-DNBV>].

<sup>163</sup> When the only patent underlying a 30-month stay is delisted, it would appear that the brand's stay terminates. See *Examining Issues Related to Competition in the Pharmaceutical Marketplace: A Review of the FTC Report, Generic Drug Entry Prior to Patent Expiration Before the Subcomm. on Health of the Comm. on Energy and Commerce House of Rep.*, 107th Cong. 69 (2002) (statement of Timothy J. Muris, Chairman, Federal Trade Commission) (suggesting that successful counterclaim to delist patent from Orange Book "would terminate



On the other hand, when there are multiple patents forming the basis for the stay, a delisting counterclaim might make less sense, as the generic may wish to litigate all the patents in a single lawsuit to streamline discovery and minimize infringement exposure.

We also suggest that the FDA supplement its regulatory efforts by providing additional detail on the patents that can be listed in the Orange Book. After the 2003 Medicare amendments, the FDA issued multiple regulations related to, among other things, the paragraph IV certification process, issuing the most recent finalized rule in October 2016.<sup>164</sup> We recommend that the FDA commence the notice-and-comment process for a proposed regulation that would designate REMS patents as a category that cannot be listed in the Orange Book. Such an amendment (with additions and ~~deletions~~) could be incorporated into the final sentence of 21 C.F.R. § 314.53(b)(1) as follows:

Process patents, patents claiming packaging, patents claiming metabolites, ~~and~~ patents claiming intermediates, and patents claiming FDA-approved Risk Evaluation and Mitigation Strategies (REMS) required under 21 U.S.C. § 355-1-(a)(1) are not covered by this section, and information on these patents must not be submitted to FDA.<sup>165</sup>

Promulgating such a rule would implement an objective of the Medicare amendments: promoting generic competition while not affecting a brand's ability to list appropriate patents claiming a drug or method of using a drug. In short, REMS patents do not appear to fall within the range of patents that can be listed in the Orange Book, and a simple regulatory amendment would make this indisputable.

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the 30-month stay"). This, however, is an open question. See Kurt R. Karst, *Does a Hatch-Waxman Patent Delisting Counterclaim Terminate a 30-Month Litigation Stay?*, FDA LAW BLOG (Nov. 8, 2012), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2012/11/does-a-hatch-waxman-patent-delisting-counterclaim-terminate-a-30-month-litigation-stay.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/11/does-a-hatch-waxman-patent-delisting-counterclaim-terminate-a-30-month-litigation-stay.html) [<https://perma.cc/57RZ-RF9U>] ("[T]he question of whether a decision on a patent delisting counterclaim is a stay-terminating decision appears to remain unanswered.").

<sup>164</sup> Abbreviated New Drug Applications and 505(b)(2) Applications, 81 Fed. Reg. 69,580, 69,580-69,658 (Oct. 6, 2016). The 2016 rule endeavors to offer generics predictability by requiring brands to clarify the scope of method-of-use patents for approved indications. For a discussion of the FDA's October 2016 regulation, see Kurt R. Karst, *FDA Issues Final Hatch-Waxman Regulations to Implement Some of the Provisions of the 2003 Medicare Modernization Act*, FDA LAW BLOG (Oct. 6, 2016, 3:10 AM), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2016/10/fda-issues-final-hatch-waxman-regulations-to-implement-some-of-the-provisions-of-the-2003-medicare-m.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2016/10/fda-issues-final-hatch-waxman-regulations-to-implement-some-of-the-provisions-of-the-2003-medicare-m.html) [<https://perma.cc/7XBW-P8J3>].

<sup>165</sup> See 21 C.F.R. § 314.53(b)(1) (2017).

B. *REMS Patent Scrutiny*

The preceding section highlighted the harms from listing inappropriate patents in the Orange Book. But even if they were not listed, a predicate question is whether the patents should have been issued in the first place. Indeed, the conclusion that a patent cannot be listed in the Orange Book does not prevent it from being asserted in litigation outside the paragraph IV context.<sup>166</sup> This section highlights significant concerns with REMS patents.

As a general matter, numerous studies have shown that many issued patents are ultimately invalidated,<sup>167</sup> with one Federal Trade Commission study finding that generics prevailed in 73% of patent challenges.<sup>168</sup> These figures are not surprising. The grant of a patent reflects an initial judgment by the PTO that an invention is patentable. But patent examiners are often unable to provide exhaustive scrutiny, with each having, on average, less than twenty hours to read an application, search for prior art, evaluate patentability, and issue conclusions.<sup>169</sup> Because of this limited examination, litigation plays a crucial role in ensuring that invalid patents do not block competition.<sup>170</sup> In *Federal Trade Commission v. Actavis, Inc.*,<sup>171</sup> the Supreme Court highlighted the “patent-related policy of eliminating unwarranted patent grants so the public will

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<sup>166</sup> THOMAS, *supra* note 88, at 420-23 (stating that, for unlistable patents, “exclusion from the Orange Book does not prevent the patent proprietor from commencing a patent infringement action against its generic competitor at such time as the cause of action bec[o]me[s] ripe,” but “owners of such patents are unable to take advantage of the dispute resolution mechanisms of the Hatch-Waxman Act” and 30-month stay).

<sup>167</sup> Empirical studies have consistently shown that at least 40% of issued patents that are litigated to decision are invalid. See John R. Allison & Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 AIPLA Q.J. 185, 194, 205 (1998) (finding that courts invalidated 46% of patents between 1989 and 1996); Kimberly A. Moore, *Judges, Juries, and Patent Cases—An Empirical Peek Inside the Black Box*, 99 MICH. L. REV. 365, 384-85 (2000) (finding that alleged infringers prevailed in 42% of patent cases that reached trial between 1983 and 1999); *Decisions for 2000-2004*, UNIV. HOUS. LAW CTR., <http://www.patstats.org/2000-04.htm> [<https://perma.cc/5DCY-7RD4>] (last visited Sept. 17, 2017) (stating that, in patent cases between 2000 and 2004, courts found 43% of patents invalid and 75% not infringed).

<sup>168</sup> The study considered paragraph IV certifications. See 21 U.S.C.A. § 355(j)(2)(A)(vii)(IV) (West 2017); *supra* notes 18-20 and accompanying text. This and the following two paragraphs are adapted from Michael A. Carrier, *A Response to Chief Justice Roberts: Why Antitrust Must Play a Role in the Analysis of Drug Patent Settlements*, 15 MINN. J.L. SCI. & TECH. 31, 34-35 (2014).

<sup>169</sup> FED. TRADE COMM’N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY 9-10 (2003), <https://www.ftc.gov/sites/default/files/documents/reports/promote-innovation-proper-balance-competition-and-patent-law-and-policy/innovationrpt.pdf> [<https://perma.cc/JCN8-57S5>].

<sup>170</sup> Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 NW. U. L. REV. 1495, 1531-32 (2001).

<sup>171</sup> 133 S. Ct. 2223 (2013).

not ‘continually be required to pay tribute to would-be monopolists without need or justification.’”<sup>172</sup>

More than 40 years earlier, in *Lear, Inc. v. Adkins*,<sup>173</sup> the Court had stated that a patent “simply represents a legal conclusion reached by the Patent Office . . . in an ex parte proceeding, without the aid of the arguments which could be advanced by parties interested in proving patent invalidity.”<sup>174</sup> Challenging invalid patents is even more important today than it was at the time the Court decided *Lear*. The burdens on the PTO have only increased, with the number of applications skyrocketing to more than 600,000 per year, more than five times the number at the time of *Lear*.<sup>175</sup>

Generics have two avenues to challenge REMS patents: district court litigation and PTO administrative proceedings. For the first 25 years after the Hatch-Waxman Act, generics primarily challenged patents in court. But after Congress’s enactment of the AIA in 2011,<sup>176</sup> generics have increasingly challenged Orange-Book-listed patents—including REMS patents—at the PTO.<sup>177</sup>

Parties in court can raise multiple challenges to REMS patents, including patentable subject matter,<sup>178</sup> novelty,<sup>179</sup> obviousness,<sup>180</sup> written description,<sup>181</sup>

<sup>172</sup> *Id.* at 2233 (quoting *Lear, Inc. v. Adkins*, 395 U.S. 653, 670 (1969)).

<sup>173</sup> 395 U.S. 653 (1969).

<sup>174</sup> *Id.* at 670; *see also* *Microsoft Corp. v. i4i Ltd.*, 564 U.S. 91, 115 (2011) (Breyer, J., concurring) (offering measures designed to “increase the likelihood that discoveries or inventions will not receive legal protection where none is due”); *United States v. Glaxo Grp., Ltd.*, 410 U.S. 52, 57 (1973) (emphasizing “public interest in free competition” in concluding that licensee in antitrust suit “may attack the validity of the patent under which he is licensed even though he has agreed not to do so in his license”).

<sup>175</sup> U.S. PATENT & TRADEMARK OFFICE, PATENT TECH. MONITORING TEAM, *U.S. Patent Statistics Chart Calendar Year 1963-2015* (June 20, 2016), [https://www.uspto.gov/web/offices/ac/ido/oeip/taf/us\\_stat.htm](https://www.uspto.gov/web/offices/ac/ido/oeip/taf/us_stat.htm) [<https://perma.cc/7WCG-8FCJ>].

<sup>176</sup> Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

<sup>177</sup> *See* Ryan Davis, *Generic Drug Patent Cases Fell by One-Third in 2016: Report*, LAW360 (Apr. 27, 2017), <https://www.law360.com/articles/918202/generic-drug-patent-cases-fell-by-one-third-in-2016-report>.

<sup>178</sup> 35 U.S.C. § 101 (2012).

<sup>179</sup> *Id.* § 102 (stating that “[a] person shall be entitled to a patent unless” the claimed invention is not novel).

<sup>180</sup> *Id.* § 103 (providing that patents will not be granted if “the claimed invention . . . would have been obvious before the effective filing date”); *KSR Int’l v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007).

<sup>181</sup> 35 U.S.C. § 112(a) (requiring specification to include written description of invention).

enablement,<sup>182</sup> best mode,<sup>183</sup> indefiniteness,<sup>184</sup> double-patenting,<sup>185</sup> and duty of disclosure.<sup>186</sup> Patentable subject matter is the broadest, and most relevant, ground to challenge REMS patents.<sup>187</sup> Section 101 of the Patent Act provides that “[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”<sup>188</sup> The Supreme Court has long held that Section 101 contains implicit exceptions against patenting laws of nature, natural phenomena, and abstract ideas.<sup>189</sup>

In *Alice Corp. v. CLS Bank International*,<sup>190</sup> the Court created a two-step test to assess ineligibility under Section 101.<sup>191</sup> First, courts are to ask whether the claims at issue are directed to a patent-ineligible concept—i.e., laws of nature, natural phenomena, or abstract ideas.<sup>192</sup> If the claims are not directed to ineligible subject matter, the patent will not be invalidated under Section 101.<sup>193</sup> But if they are so directed, then at step two courts will “examine the elements of the claim to determine whether it contains an ‘inventive concept’ sufficient to ‘transform’ the claimed abstract idea into a patent-eligible application.”<sup>194</sup> In the years since the decision, the two-step standard has led to the invalidation of numerous patents,<sup>195</sup> with one study finding that challengers won 70% of Section

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<sup>182</sup> *Id.* (mandating that specification “enable any person skilled in the art to which it pertains . . . to make and use” the invention).

<sup>183</sup> *Id.* (requiring specification to “set forth the best mode contemplated by the inventor”).

<sup>184</sup> *Id.* § 112(b) (“The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.”).

<sup>185</sup> *Id.* § 101; *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001) (“The judicially-created doctrine of obviousness-type double patenting cements [the] legislative limitation [of Section 101] by prohibiting a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.”).

<sup>186</sup> 37 C.F.R. § 1.56 (2017) (“Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office.”).

<sup>187</sup> See Jordan Paradise, *REMS as a Competitive Tactic: Is Big Pharma Hijacking Drug Access and Patient Safety?*, 15 HOUS. J. HEALTH L. & POL’Y 43, 69-76 (2015) (discussing patentability of Celgene REMS patent ’018).

<sup>188</sup> 35 U.S.C. § 101.

<sup>189</sup> *E.g.*, *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2111 (2013).

<sup>190</sup> 134 S. Ct. 2347 (2014).

<sup>191</sup> *Id.* at 2354-55.

<sup>192</sup> *Id.*

<sup>193</sup> *Id.* at 2354.

<sup>194</sup> *Id.* at 2357.

<sup>195</sup> See Ryan Davis, *Senators Express Concerns About Patent System at Hearing*, LAW360 (Apr. 25, 2017, 8:18 PM), <https://www.law360.com/articles/916462/senators-express->

101 challenges.<sup>196</sup> One principle that has emerged in recent cases is that an applicant cannot receive a patent merely by being the first to implement a known concept on a computer.<sup>197</sup>

REMS patents appear to be particularly susceptible to invalidation under *Alice*. One example is provided by U.S. Patent No. 7,668,730 (excerpted above<sup>198</sup>), which Jazz Pharmaceuticals listed in the Orange Book for Xyrem.<sup>199</sup> As the preamble to Claim 1 states, the patent is aimed at “[a] *computerized method* of distributing a prescription drug under exclusive control of an exclusive central pharmacy.”<sup>200</sup> The claimed method then provides eight steps that involve the checking of prescription, patient, and doctor information in a computer database to limit “potential abuse situations.”<sup>201</sup> Simply put, the ’730 patent is aimed at the *abstract and long-known idea* of safely dispersing prescription drugs and is put into effect merely by using *generic computer functions*.

To be sure, Section 101 does not render a patent invalid simply because claim language uses the word “computer.” For example, in *DDR Holdings, LLC v. Hotels.com*,<sup>202</sup> the Federal Circuit upheld a computer-implemented method by which the claims recited a specific manipulation of a general-purpose computer in such a way that they did not rely on a “computer network operating in its normal, expected manner.”<sup>203</sup> In contrast, the Xyrem ’730 patent contains no such manipulation of a computer process, but instead is aimed only at “[a] *computerized method* of distributing a prescription drug.”<sup>204</sup> In addition, at step

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concerns-about-patent-system-at-hearing (discussing Senate Judiciary Committee hearing on state of patent system after *Alice*).

<sup>196</sup> Robert R. Sachs, *Two Years After Alice: A Survey of the Impact of a “Minor Case” (Part 1)*, BILSKI BLOG (June 16, 2016), <http://www.bilskiblog.com/blog/2016/06/two-years-after-alice-a-survey-of-the-impact-of-a-minor-case.html> [<https://perma.cc/W8GH-L7HN>].

<sup>197</sup> *Apple, Inc. v. Ameranth, Inc.*, 842 F.3d 1229, 1243 (Fed. Cir. 2016) (“It is not enough to point to conventional applications and say ‘do it on a computer.’”).

<sup>198</sup> See *supra* note 100 and accompanying text.

<sup>199</sup> See *supra* Section II.A; see also U.S. Patent No. 7,765,106 col. 8 l. 40 (listed in Orange Book for Xyrem and claiming a method of distributing a drug using an “exclusive central computer system”); U.S. Patent No. 6,045,501 col. 2 l. 16 (listed in Orange Book for Pomalyst, Revlimid, and Thalomid and claiming a multi-step method for delivering a hazardous drug that includes “registering in a computer readable storage medium prescribers who are qualified to prescribe said drug”).

<sup>200</sup> U.S. Patent No. 7,668,730 col. 8 l. 37 (emphasis added).

<sup>201</sup> *Id.* at col. 8 l. 48 (requiring “entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations”).

<sup>202</sup> 773 F.3d 1245 (Fed. Cir. 2014).

<sup>203</sup> *Id.* at 1258-59; see also *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1335 (Fed. Cir. 2016) (finding that *Alice* does not “hold that all improvements in computer-related technology are inherently abstract” and thus patent ineligible).

<sup>204</sup> ’730 Patent col. 8 l. 37 (emphasis added).

two, the '730 patent claims do not offer an inventive concept, as they do not narrow the abstract idea of safely dispersing drugs other than by acknowledging that this would be accomplished through a computerized method.

In addition to court cases, generic firms could challenge REMS patents at the PTO<sup>205</sup>—a collateral avenue of attack that has become a popular means to call into question Orange-Book-listed patents.<sup>206</sup> The first option involves inter partes review.<sup>207</sup> A type of adversarial administrative proceeding before the Patent Trial and Appeal Board (“PTAB”), IPR has become widely utilized in the past several years.<sup>208</sup> Any third party can petition the PTO based on a patent or printed publication to review an issued patent on grounds of obviousness or lack of novelty.<sup>209</sup> For a petition to be instituted (moved forward), the petitioner must show a reasonable likelihood of success,<sup>210</sup> after which the PTAB will issue its decision.<sup>211</sup> The IPR process offers benefits that include: (1) faster times to decision and appeal, (2) a broader interpretation of claim language than would be provided in district court,<sup>212</sup> and (3) a more lenient (preponderance of the evidence) standard of review for the challenger<sup>213</sup> than the more rigorous judicial clear-and-convincing-evidence standard.<sup>214</sup>

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<sup>205</sup> This discussion is subject to potentially significant reassessment based on the Supreme Court’s forthcoming judgment on the constitutionality of IPR. *See Oil States Energy Servs., LLC v. Green’s Energy Grp., LLC*, 639 F. App’x 639 (Fed. Cir. 2016) (mem.), *cert. granted*, 2017 WL 2507340 (U.S. June 12, 2017) (No. 16-712).

<sup>206</sup> *See* 1 PATENT OFFICE LITIGATION § 21:14, Westlaw (database updated Jan. 2017) (noting that the quick “pace of an IPR . . . allows the generic the opportunity to be the aggressor” in Hatch-Waxman litigation). For a critique, see ALDEN ABBOTT ET AL., REGULATORY TRANSPARENCY PROJECT, CRIPPLING THE INNOVATION ECONOMY: REGULATORY OVERREACH AT THE PATENT OFFICE (2017), <https://regproject.org/wp-content/uploads/RTP-Intellectual-Property-Working-Group-Paper.pdf> [<https://perma.cc/E3PQ-UJX6>].

<sup>207</sup> 35 U.S.C. §§ 311-319 (2012); *see supra* text accompanying note 5.

<sup>208</sup> *See* Matthew Bultman, *AIA Petitions on Record Pace in 2017*, LAW360 (May 2, 2017, 8:15 PM), <https://www.law360.com/articles/919789/aia-petitions-on-record-pace-in-2017> (noting that in 2017 “almost 550 IPR petitions were filed during the months of January, February and March, the highest number ever in a single quarter” (emphasis omitted)).

<sup>209</sup> 35 U.S.C. § 311(a).

<sup>210</sup> *Id.* § 314(a); *see infra* note 233.

<sup>211</sup> 35 U.S.C. § 318(a) (requiring PTAB to “issue a final written decision with respect to the patentability of any patent claim challenged by the petitioner” if IPR is instituted).

<sup>212</sup> *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2136 (2016) (holding that PTO can construe challenged claims during IPR under broadest reasonable interpretation standard).

<sup>213</sup> 35 U.S.C. § 316(e).

<sup>214</sup> *Microsoft Corp. v. i4i Limited P’ship*, 564 U.S. 91, 95 (2011).

The second potential option available at the PTO is the temporary transitional covered business method review process.<sup>215</sup> Available until September 15, 2020,<sup>216</sup> CBM review provides an adversarial, administrative trial conducted before the PTAB that allows a party that has been sued to challenge a patent's validity.<sup>217</sup> Unlike IPR, which is limited to novelty and obviousness challenges, CBM allows a challenger to raise multiple grounds of patentability.<sup>218</sup> A recent study found that the PTAB has instituted more than 80% of CBM petitions based on Section 101 challenges, with 96% of the patents ultimately found unpatentable.<sup>219</sup>

Unlike IPR proceedings, pursuant to which any type of patent can be challenged, CBM review can be brought against only a "covered business method patent," which the regulations define as "a patent that claims a method or corresponding apparatus for performing data processing or other operations used in the practice, administration, or management of a financial product or service, except that the term does not include patents for technological inventions."<sup>220</sup> While the Federal Circuit has recently construed the scope of CBM review narrowly,<sup>221</sup> it has also made clear that the statute covers products outside the financial industry, which makes it a potential option for challenging REMS patents.<sup>222</sup>

REMS patents have already faced scrutiny at the PTO. After confronting litigation, generic competitors challenged all seven of the Xyrem REMS patents under both CBM review and IPR.<sup>223</sup> Before reaching the merits, the PTAB considered whether the REMS patents at issue fell within the scope of CBM review.<sup>224</sup> The PTAB ultimately concluded that they did not because only those

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<sup>215</sup> See *supra* text accompanying note 5.

<sup>216</sup> 37 C.F.R. § 42.300(d) (2017).

<sup>217</sup> *Id.* § 42.300(a).

<sup>218</sup> See *id.* § 42.304(b)(2).

<sup>219</sup> Sachs, *supra* note 196. Unlike IPR, for which the standard for instituting a petition is a reasonable likelihood that the challenged claims are unpatentable, 35 U.S.C.A. § 314(a) (West 2017), for CBM review, a petitioner must show that the claims are more likely than not unpatentable, *id.* § 324(a).

<sup>220</sup> 37 C.F.R. § 42.301.

<sup>221</sup> See *Secure Axxess, LLC v. PNC Bank Nat'l Ass'n*, 848 F.3d 1370, 1381 (Fed. Cir. 2017) (holding that method that is merely incidental to financial activity does not fall within boundaries of CBM patentability).

<sup>222</sup> *Versata Dev. Grp., Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1325 (Fed. Cir. 2015) ("[T]he definition of 'covered business method patent' is not limited to products and services of only the financial industry, or to patents owned by or directly affecting the activities of financial institutions such as banks and brokerage houses.").

<sup>223</sup> See Decision at 1, *Par Pharm., Inc. v. Jazz Pharm., Inc.*, Nos. CBM2014-00149, CBM2014-00150, CBM2014-00151, CBM2014-00153 (P.T.A.B. Jan. 13, 2015), 2015 WL 216987.

<sup>224</sup> *Id.* at \*4.

method patents claiming, among other things, the “management of a financial product or service” could be reviewed under the program.<sup>225</sup> In the PTAB’s opinion, the Xyrem REMS patents were aimed at only a method of controlling access to a drug to guard against abuse rather than “recit[ing] or requir[ing] an activity involving the movement of money or extension of credit in connection with the sale of a prescription drug.”<sup>226</sup>

IPR proceedings proved more hospitable to challenges to the Xyrem patents. In that setting, the generics raised as prior art materials used by the FDA in a committee meeting before Xyrem’s approval.<sup>227</sup> This meeting, which covered issues relating to Xyrem’s safety and abuse potential,<sup>228</sup> occurred on June 6, 2001, 18 months before the parent application of the Xyrem patents was filed on December 17, 2002.<sup>229</sup> Given the purpose of that meeting, Xyrem’s sponsor submitted materials explaining how it would mitigate the potential for abuse.<sup>230</sup> The PTAB ultimately agreed with the generics’ contention that the meeting materials constituted prior art rendering the Xyrem REMS patents invalid.<sup>231</sup>

In addition to challenging patentable subject matter, generics also contended that the Xyrem patent was obvious due to the combination of Celgene’s ’501 REMS patent and a published interview of brand-firm representatives.<sup>232</sup> While the PTO did not agree and instituted IPR on other grounds,<sup>233</sup> the potential for overlapping disclosures between REMS patents presents an obviousness argument available to future challengers.

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<sup>225</sup> *Id.* at \*6-7.

<sup>226</sup> *Id.* at \*6.

<sup>227</sup> *See* Petition for IPR at 11-12, *Amneal Pharm., Inc. v. Jazz Pharm., Inc.*, No. IPR2015-00546 (P.T.A.B. filed Jan. 8, 2015), 2015 WL 113762 (contending that materials used during FDA advisory committee meeting convened as prerequisite to granting approval of Xyrem “either teach[] or render[] obvious every limitation of the challenged claims”).

<sup>228</sup> *Id.* at 12, 14 n.1, 18 n.4 (describing materials reviewed by advisory committee).

<sup>229</sup> *Id.* at 11, 13.

<sup>230</sup> *Id.* at 3-4.

<sup>231</sup> *E.g.*, Final Written Decision, *Par Pharm., Inc. v. Jazz Pharm., Inc.*, No. IPR2015-00546 (P.T.A.B. July 27, 2016), 2016 WL 7998375, at \*21 (invalidating Celgene’s ’106 patent as obvious); *see also* Petition for IPR, *Amneal v. Jazz*, *supra* note 227, at 3-4 (noting that “the general mitigation of risks . . . was well-established in the art before the earliest effective filing date of the ’106 patent”).

<sup>232</sup> *See* Decision, *Amneal Pharm., LLC v. Jazz Pharm., Inc.*, No. IPR2015-00545 (P.T.A.B. July 29, 2015), 2015 WL 9899012, at \*18-21 (instituting IPR proceedings on Jazz Pharmaceuticals’ ’182 patent listed for Xyrem).

<sup>233</sup> *Id.* “Institution” refers to the preliminary decision of a three-judge panel to initiate an IPR trial. In such a case, the petitioner must show a reasonable likelihood of success with respect to at least one of the claims challenged in the IPR petition. 35 U.S.C. § 314(a) (2012).



In another case, a successful IPR challenge was launched against two of Celgene's REMS patents. In this case, controversial hedge fund manager Kyle Bass<sup>234</sup> challenged the '501 and '720 patents through IPR proceedings.<sup>235</sup> In October 2016, the PTO concluded that both REMS patents were unpatentable based on prior art references discussing, among other things, the role of pharmacists in controlling the distribution of a hazardous drug while minimizing the risk posed to pregnant women.<sup>236</sup>

Looking forward, litigation concerning REMS patents can take multiple forms. First is CBM review. Even though the PTO did not allow such review of the Xyrem patents to proceed, it did not categorically prohibit the use of CBM to challenge REMS patents. Instead, the PTO raised six possible claim limitations that *could* bring a REMS patent into CBM review, namely:

- (i) the sale of a prescription drug, (ii) processing of payments, benefits, or insurance claims related to the sale of a prescription drug, (iii) a method of insuring a patient or determining the cost of insurance, (iv) a method of determining the cost of prescription benefits, (v) a method of facilitating payment of health care benefits, or (vi) the extension of credit for the purchase of a prescription drug.<sup>237</sup>

In the future, any REMS patents that include such limitations could be subject to CBM review. And such review could consider arguments relating to patentable subject matter, novelty, obviousness, enablement, and double patenting.<sup>238</sup>

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<sup>234</sup> Kyle Bass famously has used IPR proceedings to challenge pharmaceutical patents after shorting the stock of the targeted company. See Carl J. Minniti III, *The Big (Patent) Short*, RUTGERS INST. FOR INFO. POLICY & LAW (Mar. 8, 2016), <http://riipl.rutgers.edu/the-big-patent-short/> [<https://perma.cc/X97H-DZ8S>] (describing Bass's strategy of shorting stock of "publicly traded biotech firm[s] whose revenues are concentrated on a particular drug" and then using Coalition for Affordable Drugs to invoke IPR to challenge validity of patents covering drug).

<sup>235</sup> E.g., Decision, Coalition for Affordable Drugs VI LLC v. Celgene Corp., No. IPR2015-01092 (P.T.A.B. Oct. 27, 2015), 2015 WL 6506488 (instituting IPR of Celgene's '501 patent).

<sup>236</sup> E.g., Final Written Decision, Coalition for Affordable Drugs VI LLC v. Celgene Corp., No. IPR2015-01103 (P.T.A.B. Oct. 26, 2016) (finding Celgene's '720 patent invalid on grounds of obviousness); see also Ryan Davis, *Kyle Bass Gets More Wins as PTAB Axes Celgene Patents*, LAW360 (Oct. 27, 2016, 5:40 PM), <https://www.law360.com/articles/856460/kyle-bass-gets-more-wins-as-ptab-axes-celgene-patents> ("The PTAB . . . found that since the prior art described ways of controlling access to different potentially hazardous drugs, it would have been obvious to apply those features to controlling thalidomide.").

<sup>237</sup> Decision, Par Pharm., Inc. v. Jazz Pharm., Inc., Nos. CBM2014-00149, CBM2014-00150, CBM2014-00151, CBM2014-00153 (P.T.A.B. Jan. 13, 2015), 2015 WL 216987, at \*6.

<sup>238</sup> See 1 PATENT OFFICE LITIGATION § 3:20, Westlaw (database updated Jan. 2017) (outlining scope of CBM review).

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If a generic is unsuccessful in obtaining CBM review or a REMS patent is not amenable to Section 101 scrutiny, it could pursue an obviousness challenge through the IPR process. As seen with the Xyrem IPRs, a brand sponsor may have divulged risk mitigation materials to the FDA before applying for a REMS patent. Indeed, when a brand develops multiple REMS programs to obtain FDA approval, it does not know which program the agency will accept.<sup>239</sup> One example appears with Jazz Pharmaceuticals' and the FDA's negotiation of the Xyrem REMS, with the parties negotiating for six years about changes to Xyrem's program, including whether the drug needed to be dispensed through a single pharmacy.<sup>240</sup>

As a result, if a brand seeks to patent a program it already disclosed in an FDA meeting, that would create the prior art that would prevent the patent's issuance. And even if this is not the case, brands may not know which REMS program the FDA will accept, which could lead them to preemptively prosecute a broad claim scope that could ensnare the to-be-determined REMS program.

Another line of attack challenging REMS patents' obviousness could be found in the Federal Circuit's opinion in *Ormco Corp. v. Align Technology, Inc.*<sup>241</sup> In that case, the court observed that food-and-drug law and regulations contain instructions for using medical devices. Because such regulations "supply ample evidence of a motivation to provide instructions as to how to use the devices,"<sup>242</sup> claim limitations based on such instructions would not render the challenged claim nonobvious.<sup>243</sup> To similar effect, generics could use *Ormco* to show obviousness when a claim is based on instructions in a REMS program.

Future obviousness arguments may rely on prior art consisting of REMS patents that have already been issued. Indeed, as time goes by, future REMS patents will be required to avoid unpatentability in light of an expanding universe of patents claiming broad methods of REMS distribution processes. While such patents may be narrowly tailored to the distribution of a specific drug (as with the Entereg patents), obviousness arguments based on a combination of previous REMS patents and literature explaining the dangers of specific drugs may be successful. And even though obviousness challenges are based on the

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<sup>239</sup> FDA, BRIEF OVERVIEW, *supra* note 40, at 4 (reiterating that the FDA reviews and approves brands' REMS).

<sup>240</sup> Trueman W. Sharp, *Decision to Waive the Requirement for a Single, Shared System REMS for Sodium Oxybate Oral Solution*, at 5-7 (Jan. 17, 2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/UCM538244.pdf> [<https://perma.cc/5S5F-L2SN>]. The FDA believed a single pharmacy was not necessary and would burden the healthcare system and patient access. *Id.* at 5-6. The agency eventually approved the REMS due to the amount of resources expended, the burden of changing an existing RiskMAP, and the limited number of drugs affected. *Id.* at 7-8.

<sup>241</sup> 463 F.3d 1299, 1309 (Fed. Cir. 2006).

<sup>242</sup> *Id.*

<sup>243</sup> *Id.*

individual facts underlying each patent, the arguments we have discussed and recent history with the Xyrem and Celgene REMS patents point the way toward invalidation.

While many REMS patents appear to be invalid, another relevant question involves the range of remedies available for valid and infringed patents. We explore this question next.

### C. Damages Remedy

For valid patents that have been infringed, courts must select an appropriate remedy.<sup>244</sup> In *eBay Inc. v. MercExchange, L.L.C.*,<sup>245</sup> the landmark ruling on this issue, the Supreme Court articulated a four-factor test requiring a plaintiff to demonstrate:

- (1) that it has suffered an irreparable injury;
- (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury;
- (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and
- (4) that the public interest would not be disserved by a permanent injunction.<sup>246</sup>

In *eBay*, the Court found that “the Patent Act expressly provides that injunctions ‘may’ issue ‘in accordance with the principles of equity.’”<sup>247</sup> And it made clear that such discretion is not limited by the property attributes of patents, as “the creation of a right is distinct from the provision of remedies for violations of that right.”<sup>248</sup>

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<sup>244</sup> In this section, we assume a generic has succeeded in delisting a REMS patent from the Orange Book and the underlying litigation has been brought under 35 U.S.C. § 271(a) and (b) (direct and indirect infringement) rather than under the Hatch-Waxman Act, 35 U.S.C. § 271(e), which provides different remedies. See Barr et al., *supra* note 133, § 12.V.B (discussing statutory differences between injunctive relief available under Patent Act and Hatch-Waxman Act).

<sup>245</sup> 547 U.S. 388 (2006). Even though we assume that an asserted REMS patent has been delisted, we note that *eBay* applies to not only § 271(a)-(c) (direct and indirect infringement) but also § 271(e)(4) (the Hatch-Waxman remedy provision). See, e.g., Bayer Pharma AG v. Watson Labs., Inc., No. 12-1726, 2016 WL 7468172, at \*3 (D. Del. Dec. 28, 2016) (applying *eBay* and declining to impose injunction under § 271(e)(4)); Alcon, Inc. v. Teva Pharm. USA, Inc., No. 06-0234, 2010 WL 3081327, at \*3 (D. Del. Aug. 5, 2010) (applying *eBay* and declining to grant brand’s request for injunction); Pfizer Inc. v. Apotex Inc., 731 F. Supp. 2d 754, 760-62 (N.D. Ill. 2010) (rejecting brand’s argument that automatic injunction should be awarded in Hatch-Waxman cases).

<sup>246</sup> *eBay*, 547 U.S. at 391.

<sup>247</sup> *Id.* at 391-92 (quoting 35 U.S.C. § 283).

<sup>248</sup> *Id.* at 392.

Whether a patentee must show that the four factors, *on balance*, favor injunctive relief or prevail on *each* of the factors remains an open question. In *Nichia Corp. v. Everlight Americas*,<sup>249</sup> the Federal Circuit took the latter position, holding that a patentee “must prove that it meets all four equitable factors.”<sup>250</sup> The court found that because the patentee “failed to establish one of the four equitable factors, the [lower] court did not abuse its discretion in denying [the patentee’s] request for an injunction.”<sup>251</sup>

The first factor, irreparable harm, is more likely to be found where the parties are direct competitors.<sup>252</sup> Typically, competition between patent holders and alleged infringers suggests irreparable harm since a patent “enjoys its highest value when it is asserted against a direct competitor in the [patentee’s] market.”<sup>253</sup> In the pharmaceutical industry, brands and generics generally compete, and (in large part because of state substitution laws) when generics enter the market, the brand price tends to rapidly decline.<sup>254</sup> The regulatory regime, however, makes this conclusion more nuanced than the typical setting. Here, the Hatch-Waxman Act and state substitution laws are based on a generic’s therapeutic equivalence to the brand and result in price erosion.<sup>255</sup> In contrast, a patented REMS program is separate from this process, not claiming the drug or playing a role in the price reductions flowing from substitution laws.

The Federal Circuit has highlighted the importance of showing a “causal nexus between [the] infringing conduct and [the] alleged harm.”<sup>256</sup> This nexus is important to ensure there is “some connection” between the two.<sup>257</sup> In fact, “[w]ithout a showing of causal nexus, there is no relevant irreparable harm.”<sup>258</sup> In addition, as Justice Kennedy explained in his *eBay* concurrence:

When the patented invention is but a small component of the product the companies seek to produce and the threat of an injunction is employed simply for undue leverage in negotiations, legal damages may well be

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<sup>249</sup> 855 F.3d 1328 (Fed. Cir. 2017).

<sup>250</sup> *Id.* at 1341.

<sup>251</sup> *Id.* at 1344.

<sup>252</sup> *E.g.*, *Advanced Cardiovascular Sys., Inc. v. Medtronic Vascular, Inc.*, 579 F. Supp. 2d 554, 558, 559 (D. Del. 2008) (stating that “[c]ourts awarding permanent injunctions typically do so under circumstances where plaintiff practices its invention and is a direct market competitor” but finding absence of irreparable harm since “there is no indication that [the alleged infringer] is currently drawing . . . sales away from [the patentee]”).

<sup>253</sup> *See Visto Corp. v. Seven Networks, Inc.*, No. 2:03-cv-00333, 2006 WL 3741891, at \*4 (E.D. Tex. Dec. 19, 2006); *see also Janssen Products, L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 697 (D.N.J. 2014), *modified*, 2016 WL 1029269 (D.N.J. Mar. 15, 2016).

<sup>254</sup> *E.g.*, GPHA REPORT, *supra* note 27, at 7.

<sup>255</sup> *See supra* notes 21-23 and accompanying text.

<sup>256</sup> *Apple Inc. v. Samsung Inc.*, 735 F.3d 1352, 1363-64 (Fed. Cir. 2013).

<sup>257</sup> *Id.* at 1364.

<sup>258</sup> *Id.* at 1363.

sufficient to compensate for the infringement and an injunction may not serve the public interest.<sup>259</sup>

In this case, there does not appear to be a causal nexus between the infringing conduct (infringement of a patented REMS program) and the alleged harm (price erosion resulting from automatic substitution laws).<sup>260</sup> Substitution laws rely on therapeutic equivalence rather than REMS programs, which merely specify means to mitigate the risks of dangerous drugs. To find a causal nexus here would mean that any reason a generic reaches the market constitutes sufficient grounds to satisfy the irreparable-harm hurdle. That is the type of presumption that *eBay* rejected.

In addition to lacking a causal nexus, the REMS program resembles the “small component” highlighted by Justice Kennedy, playing little role in generic price erosion. Unlike the molecule or formulation, which make up the product itself, REMS are not an essential component of a brand drug. Infringement of the molecule or formulation provides a causal link to state substitution laws since a generic will not be deemed equivalent if it does not copy the molecule or formulation. In contrast, infringing a REMS patent does not result in “[the generic’s] entire product[] infring[ing] . . . [the brand’s] entire product”<sup>261</sup> by way of a molecule or formulation that is far more than “a small component”<sup>262</sup> of the generic product. These observations—that there is no causal nexus and that a REMS program is a small component—reflect infringement arising merely from compliance with the REMS regime rather than unjustifiable free-riding that creates irreparable harm.<sup>263</sup>

Applying the second factor, monetary damages provide adequate compensation. One crucial element is patent licensing.<sup>264</sup> Of relevance here,

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<sup>259</sup> *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 396-97 (2006) (Kennedy, J., concurring).

<sup>260</sup> Further upstream, price reductions also flow from the Hatch-Waxman Act, which allows generics to piggyback on brand firms’ clinical trials. *See supra* notes 20-23 and accompanying text.

<sup>261</sup> *Endo Pharms. Inc. v. Amneal Pharms., LLC*, No. 12-8115 (S.D.N.Y. Apr. 29, 2016), 2016 WL 1732751, at \*5 (omnibus opinion).

<sup>262</sup> *Id.*

<sup>263</sup> In addition, the claim that the denial of an injunction would lead to irreparable harm is weakened by statutorily mandated intrusions on the right to exclude, which require brands to: (1) permit experimentation during the patent term, 35 U.S.C. § 271(e)(1) (2012); (2) allow generics to piggyback on clinical trials, *see supra* notes 20-23 and accompanying text; (3) witness substitution at the pharmacy counter, *see supra* notes 24-26 and accompanying text; and (4) not block or delay generics, 21 U.S.C.A. § 355-1(f)(8) (West 2017). *See also* Carrier, *supra* note 12, at 45, 62 (noting that the Hatch-Waxman Act provides brands with significant benefits including patent term extensions, nonpatent market exclusivity, and automatic 30-month stays).

<sup>264</sup> *Advanced Cardiovascular Sys., Inc. v. Medtronic Vascular, Inc.*, 579 F. Supp. 2d 554, 560 (D. Del. 2008).

when a brand and generic each offer a REMS program, the FDAAA requires them to create a shared REMS,<sup>265</sup> with Congress anticipating that brands would license their REMS patents to generics.<sup>266</sup> The propriety of a damages remedy is confirmed by the legislature's instruction that brands could not use REMS programs to "block or delay" generic approval.<sup>267</sup> Because an injunction would lead directly to such prohibited blocking or delaying, awarding damages would be consistent with Congress's intentions.

Intent is the final factor relevant to the adequacy of damages. In *TruePosition Inc. v. Andrew Corp.*,<sup>268</sup> for example, the court found that this factor favored an injunction because the infringement was willful,<sup>269</sup> with the defendant infringing for six years.<sup>270</sup> In contrast, a generic in the REMS setting is required to implement the brand's program. This demonstrates the *opposite* of willful conduct since the regulatory regime specifically *requires* the generic to imitate the brand version.

Third, the balancing of hardships confirms the inaptness of an injunction. When a brand has a REMS, generic approval is conditioned on having an equivalent REMS program.<sup>271</sup> If a generic is prevented from using the program, patients would be denied the opportunity to purchase low-cost drugs due to the patenting of a government-mandated safety program designed to open access to drugs otherwise too dangerous to enter the market. In other words, the rock of FDA regulations and hard place of patent law will have combined to squeeze out competition. Given the FDA's requirement that the programs be the same, generics do not have flexibility to adopt a different REMS program.

At the same time, a brand's argument based on the need for an injunction to protect innovation incentives is questionable. As discussed in more detail in the next Section,<sup>272</sup> brands do not appear to need significant incentives to receive patents on computer-implemented methods required by the FDA, as confirmed

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<sup>265</sup> 21 U.S.C.A. § 355-1(i)(1)(B).

<sup>266</sup> In cases involving patented REMS, Congress expected brands to license their patents. *See id.* § 355-1(i)(B)(ii) (providing for shared REMS and allowing generic to create separate REMS when it "was unable to obtain a license").

<sup>267</sup> *Id.* § 355-1(f)(8).

<sup>268</sup> 568 F. Supp. 2d 500 (D. Del. 2008).

<sup>269</sup> *Id.* at 532.

<sup>270</sup> *Muniauction, Inc. v. Thomson Corp.*, 502 F. Supp. 2d 477, 483 (W.D. Pa. 2007), *rev'd in part, vacated in part*, 532 F.3d 1318 (Fed. Cir. 2008).

<sup>271</sup> The FDA has made clear that if generics and brands cannot successfully negotiate shared REMS, the programs will be "equal." STAFF OF S. COMM. ON AGING, *supra* note 61, at 116 ("Well, the part of the REMS provision that requires a single shared system, as a practical matter, we have to try and try and try and try, and then finally, we declare defeat and we go ahead and let the generic have their own system that is separate but equal." (quoting Dr. Janet Woodcock, Director, FDA Center for Drug Evaluation and Research)); *see also supra* note 60 and accompanying text.

<sup>272</sup> *See infra* notes 287-89 and accompanying text.

by the relative lack of patenting of REMS programs. In short, generics enjoined from the market suffer more hardship than brands receiving damages.

Nor is an additional issue that favors an injunction—a defendant’s ability to easily modify its product to avoid infringement—present here. In *TiVo Inc. v. Echostar Communications*,<sup>273</sup> for example, the court awarded an injunction in part because the defendant could have transmitted software updates to its products that would have disabled the infringing features.<sup>274</sup> In contrast, here the generic is not able to easily modify its product to avoid infringement because the FDA requires that the generic’s REMS program be the same as the brand’s program.

For the fourth factor, the public interest also weighs in favor of awarding damages. As discussed below, innovation incentives are not crucial in this setting, while access to drugs is.<sup>275</sup> Again, Congress specifically prohibited brand firms from “block[ing] or delay[ing]” generic approval,<sup>276</sup> and the public benefits from having multiple, safely distributed drugs on the market subject to a single, shared REMS. In fact, four of the nine post-*eBay* cases in which the Federal Circuit has affirmed the denial of an injunction have concerned medical device technology.<sup>277</sup> In *Bard Peripheral Vascular, Inc. v. W.L. Gore & Associates*,<sup>278</sup> for example, the Federal Circuit affirmed the district court’s denial of an injunction, finding that “it was in the public interest to allow competition in the medical device arena.”<sup>279</sup>

Here, REMS programs ensure drug safety. A brand firm is required to create the program as a condition of it being on the market at all.<sup>280</sup> The setting is similar to the medical-device cases in which competition is important for safety reasons. It is not in the public interest for brands to obtain injunctions against

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<sup>273</sup> 446 F. Supp. 2d 664 (E.D. Tex. 2006).

<sup>274</sup> *Id.* at 670; *see also* *Transocean Offshore Deepwater Drilling, Inc. v. GlobalSantaFe Corp.*, No. H-03-2910, 2006 WL 3813778, at \*6 (S.D. Tex. Dec. 27, 2006) (noting that senior official conceded company had several options to avoid infringement, one of which would have been “minimally disruptive”).

<sup>275</sup> *See infra* notes 287-89 and accompanying text.

<sup>276</sup> 21 U.S.C.A. § 355-1(f)(8) (West 2017).

<sup>277</sup> Ryan T. Holte & Christopher B. Seaman, *Patent Injunctions on Appeal: An Empirical Study of the Federal Circuit’s Application of eBay*, 92 WASH. L. REV. 145, 196 (2017).

<sup>278</sup> 670 F.3d 1171 (Fed. Cir. 2012).

<sup>279</sup> *Id.* at 1192; *see also* *Hypoxico, Inc. v. Colorado Altitude Training LLC*, 608 F. App’x 946 (Fed. Cir. 2015); *Tyco Healthcare Grp. LP v. Applied Med. Res. Corp.*, 579 F. App’x 1005 (Fed. Cir. 2014); *Voda v. Cordis Corp.*, 536 F.3d 1311, 1329 (Fed. Cir. 2008); *Advanced Cardiovascular Sys., Inc. v. Medtronic Vascular, Inc.*, 579 F. Supp. 2d 554, 561 (D. Del. 2008) (“A strong public interest in maintaining diversity in the coronary stent market has been previously recognized by this court and the Federal Circuit.”).

<sup>280</sup> 21 U.S.C.A. § 355-1(a)(1) (requiring submission of proposed REMS for initial approval).

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generic REMS programs, which are mandated by the FDA and which reflect vital policies of safety and patient access.<sup>281</sup>

In short, the second, third, and fourth factors weigh strongly against an injunction: the statute anticipates licensing and mandates that the brand not block or delay entry, and the balance of hardships and public interest both favor damages. The competitive relationship makes the first factor a closer call, but it is counterbalanced by the required equal nature of REMS programs. Courts, in other words, should award damages in the case of infringement. And because the brand would, at a minimum, not be able to satisfy the second, third, and fourth factors, this conclusion is even stronger under the *Everlight* analysis that requires a patentee to satisfy each of the four factors.

#### D. *REMS Patent Mitigation*

Our fourth proposal recommends that Congress mitigate REMS patents through amendments to the FDAAA. This recommendation is based on the role of REMS patents in the regulatory system, the limited need for these patents, and their significant potential to block generic entry.

First, because the drugs cannot enter the market without FDA approval, REMS programs present a type of quasi-regulation.<sup>282</sup> In that respect, the effect of REMS programs resembles laws pertaining to the pharmaceutical marketing of controlled substances. The Combat Methamphetamine Epidemic Act of 2005 (“CME”)<sup>283</sup> bans over-the-counter sales of cold medicines containing pseudoephedrine and imposes obligations on pharmacies selling packages containing more than sixty milligrams of pseudoephedrine, including requiring, among other things, that pharmacies maintain a “logbook” of sales by identifying “products by name, the quantity sold, the names and addresses of purchasers, and the dates and times of the sales.”<sup>284</sup>

In this setting, it would be concerning if one pharmacy enforced a patent against another on a method of distributing pseudoephedrine that did nothing more than adopt the statutory language of the CME words verbatim because this would create a bottleneck of compliance with the law, effectively negating the statute’s objective of safely and uniformly distributing pseudoephedrine. But that is exactly what is occurring in the REMS setting, as a comparison of the Entereg patent claims and REMS program described above in Table 2 suggests. If the FDA were to mandate a shared system with the Entereg REMS program, the generic would not be able to adopt the program without infringing the Entereg REMS patent. As a result, the same outcome as the hypothetical CME

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<sup>281</sup> *Id.* § 355-1(f)(2)(C).

<sup>282</sup> We consider REMS to be a “quasi-regulation” because without FDA approval of a REMS program, a drug cannot be marketed.

<sup>283</sup> Pub. L. No. 109-177, tit. VII, 120 Stat. 192, 256 (2006) (codified as amended in scattered sections of 21, 22, 28, 42, and 49 U.S.C.).

<sup>284</sup> 21 U.S.C. § 830(e)(1)(A)(iii) (2012).



scenario would occur, negating Congress's objective of promoting uniform and safe risk mitigation.

To be sure, there are differences between mandating a REMS program and regulating controlled substances. When first adopted, REMS programs are individualized and drafted by the regulated party, while a statute limiting over-the-counter distribution is generally applicable to a class of drugs. But when a generic files its application under section 355(j)<sup>285</sup> referencing a drug with an approved REMS, the FDAAA requires the ANDA and listed drug to use an SSRS.<sup>286</sup>

As a result, REMS act as quasi-regulations mandating a shared system as a prerequisite to approval, similar to how the CME mandates that pharmacies follow methods of distributing pseudoephedrine to avoid civil or criminal penalties. In short, obtaining patents on government-imposed obligations raises significant concerns.

Second, from an incentives standpoint, the protection of a general computerized method of communicating with a pharmacy does not appear to require a 20-year right to exclude. As described above, these patents cover general computer-implemented methods used to keep track of the recipient of a particular drug. Indeed, many REMS patents have already been successfully challenged at the PTO. And many of the patents, granted before the *Alice* and *Mayo* decisions and thus examined under different analyses than when they were granted, likely would be invalidated today.<sup>287</sup>

The questionable need to provide incentives is confirmed by the relative absence of REMS patents. Brand firms often obtain patents on multiple aspects of drugs, including active ingredients, formulations, polymorphs, methods of treatment, and additional elements.<sup>288</sup> In contrast, brands typically have not patented their REMS programs. Of the 62 NDAs with a REMS program, only 5 have involved patents on REMS elements. For the 5 REMS-patented drugs, 23 REMS patents have been listed, less than 5% of the 506 patents listed for the 62 drugs. These figures speak volumes in an industry in which (outside the REMS setting) brand firms have few qualms seeking numerous patents for their drugs.

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<sup>285</sup> 21 U.S.C.A. § 355-1(j).

<sup>286</sup> *Id.* § 355-1(i)(1)(B)(ii).

<sup>287</sup> For a discussion of the application of more-recently-decided caselaw to previously-issued patents, see Gene Quinn, *Retroactive Changes to Patent Eligibility Law Suggests Patent Are Not a Property Right*, IPWATCHDOG (Apr. 6, 2015), <http://www.ipwatchdog.com/2015/04/06/retroactive-patent-eligibility-patents-not-a-property-right/id=56205/> [<https://perma.cc/B5XE-6MS8>]. In addition, REMS patents would appear to bear a closer resemblance to patents on secondary advances (like formulations and compositions), which one study found are upheld only 32% of the time, than to patents on active ingredients, which are upheld in 92% of cases. C. Scott Hemphill & Bhaven Sampat, *Drug Patents at the Supreme Court*, 339 SCIENCE 1386, 1387 (2013) (examining completed patent litigation on drugs first eligible for challenges between 2000 and 2008).

<sup>288</sup> See generally Barr et al., *supra* note 133, § 7.

Would brand firms stop innovating if REMS patents could no longer be used to block or delay generics? We think not. In many cases, brands are not even aware that a REMS program will be required, as the FDA can impose REMS after the drug is already on the market.<sup>289</sup> If a brand obtains a REMS patent after a drug enters the market, it is hard to see how the patent was the reason the drug was developed.

In *SmithKline Beecham Consumer Healthcare v. Watson Pharmaceuticals*,<sup>290</sup> the Second Circuit offered support for such a conclusion in rejecting a copyright infringement claim based on a brand's label that the generic needed to copy in order to comply with the Hatch-Waxman Act.<sup>291</sup> The court found that "the profit sought by the creator of the pioneer drug label flows primarily from the administrative approval of the drug and the patent and exclusivity periods . . . that follow."<sup>292</sup> The court also noted that "[t]he pertinent purpose of the copyright laws—to encourage the production of creative works . . . is not seriously implicated by allowing the 'same' labeling requirement to trump a copyright under the Hatch-Waxman [Act]."<sup>293</sup> Finally, the court concluded that "[i]t is simply not conceivable that, if we reject [the brand firm's] claim, pioneer drug producers will so fear the copying of labels by future generic drug producers that some pioneer producers—or even one of them—will lack the incentive to create labeling needed for FDA approval."<sup>294</sup>

Third, in addition to the questionable need to provide incentives, REMS patents can prevent drugs from reaching the market. The regulatory regime underscores the importance of widespread generic competition. In the Hatch-Waxman Act,<sup>295</sup> Congress offered several mechanisms to increase generic competition, such as experimentation on brand drugs during the patent term.<sup>296</sup> And substitution laws, in effect in all 50 states today, allow (and often require) pharmacists to substitute generic versions of brand drugs absent a doctor's contrary instructions.<sup>297</sup>

Even more directly relevant to REMS programs, the FDAAA authorized the FDA to require REMS but did not allow brands to "block or delay" generic

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<sup>289</sup> 21 U.S.C.A. § 355-1(a)(1), (a)(2)(A).

<sup>290</sup> 211 F.3d 21 (2d Cir. 2000).

<sup>291</sup> *Id.* at 29.

<sup>292</sup> *Id.*

<sup>293</sup> *Id.* (citations omitted).

<sup>294</sup> *Id.*

<sup>295</sup> Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355).

<sup>296</sup> 35 U.S.C. § 271(e)(1) (2012) ("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 . . .").

<sup>297</sup> Carrier, *supra* note 24, at 1017.

entry.<sup>298</sup> Congress also sought to ensure that REMS programs do not burden patients who “have difficulty accessing health care (such as patients in rural or medically underserved areas)” or those with “serious or life-threatening diseases or conditions.”<sup>299</sup> Finally, when brands and generics each have REMS programs, shared systems reduce the burdens on healthcare providers and manufacturers but will not be used when the FDA is forced to grant a waiver because of a failure to negotiate a patent license. In short, the pharmaceutical regime reveals the importance of generic competition and the concern with REMS patents.

The *SmithKline* court highlighted the importance of a statute’s objectives, recognizing that “[t]he purposes of the Hatch-Waxman [Act] would be severely undermined if copyright concerns were to shape the FDA’s application of the ‘same’ labeling requirement.”<sup>300</sup> The court explained that the Act was “intended to facilitate the introduction of generic competitors” by allowing them to “piggy-back” on the brand’s application.<sup>301</sup> If labels “substantially similar” to “copyrighted labels on pioneer drugs had to be avoided, the administrative process of approving a new label would . . . drain the resources of the FDA and generic producer[s].”<sup>302</sup> Avoiding infringement also would “delay the introduction of the generic product without advancing public health and safety to any perceptible degree.”<sup>303</sup> In “adopt[ing] the ‘same’ labeling requirement . . . Congress left no room for such redundant proceedings,” which meant that “[t]he FDA cannot be faithful to that requirement . . . without requiring labels that will often violate copyrights.”<sup>304</sup> And “[i]f copyright law were to prevail,” the court concluded, “producers of generic drugs [would] always be delayed in—and quite often prohibited from—marketing the generic product . . . at great odds with the purposes of the Hatch-Waxman [Act].”<sup>305</sup>

Like the Hatch-Waxman Act, the FDAAA fostered important policy goals. It promoted drug safety through uniform programs to combat drug risks<sup>306</sup> while making clear that REMS programs could not be used to block or delay generic entry.<sup>307</sup> In allowing brands to exclude generics, patent law conflicts with the

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<sup>298</sup> 21 U.S.C.A. § 355-1(f)(8) (West 2017) (“No holder of an approved covered application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application . . . or to prevent application of such element . . . to a drug that is the subject of an abbreviated new drug application.”).

<sup>299</sup> *Id.* § 355-1(f)(2)(C).

<sup>300</sup> *SmithKline Beecham Consumer Healthcare v. Watson Pharms.*, 211 F.3d 21, 28 (2d Cir. 2000).

<sup>301</sup> *Id.*

<sup>302</sup> *Id.*

<sup>303</sup> *Id.*

<sup>304</sup> *Id.*

<sup>305</sup> *Id.*

<sup>306</sup> For a discussion of the overlap between brand and generic REMS, see *supra* notes 115-17 and accompanying text.

<sup>307</sup> 21 U.S.C.A. § 355-1(f)(8) (West 2017).

FDAAA. Similar to the finding that “[t]he creation of labels to be approved by the FDA . . . is ancillary to the [agency’s] administrative process,”<sup>308</sup> innovation in the context of REMS patents is a secondary consideration in the setting of FDA-mandated risk programs.<sup>309</sup>

A final questionable aspect appears in the efforts of REMS patent holders to use the FDA process to shepherd generics into the scope of their patents. For example, when the FDA was considering granting a waiver from a shared REMS system to generics referencing Xyrem—which used “certified pharmacies”<sup>310</sup>—Jazz argued against a waiver “for generics that utilize[] multiple pharmacies, instead of a single, central pharmacy.”<sup>311</sup> Not coincidentally, four of the seven Xyrem REMS patents included a “central pharmacy” as a claim limitation.<sup>312</sup> In other words, Jazz appeared to use the FDA process to sweep generics into the grasp of their centralized-pharmacy patent.

In short, there is little need to provide incentives for REMS patents, especially in the setting of a government-mandated safety program that can impose a rigid bottleneck. We therefore propose the following amendments to the FDAAA, which would mitigate the most concerning aspects of REMS patents and ensure that they do not block or delay generic competition:

21 U.S.C. § 355-1(f)(8):

“No holder of an approved covered application shall use any element to assure safe use, whether patented or not, required by the Secretary under this subsection to block or delay approval . . . .”

21 U.S.C. § 355-1(i)(1)(B)(ii):

“[A]n aspect of the elements to assure safe use for the applicable listed drug ~~is claimed by a patent that has not expired or~~ is a method or process that, as a trade secret, is entitled to protection, and the applicant for the abbreviated new drug application certifies that it has sought a license for use of an aspect of the elements to assure safe use for the applicable listed drug and that it was unable to obtain a license.

A certification under clause (ii) shall include a description of the efforts made by the applicant for the abbreviated new drug application to obtain a license. In a case described in clause (ii), the Secretary may seek to negotiate a voluntary agreement with the owner of the trade secret

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<sup>308</sup> *SmithKline*, 211 F.3d at 28.

<sup>309</sup> FDA, BRIEF OVERVIEW, *supra* note 40, at 4.

<sup>310</sup> West-Ward Pharm. Corp., Sodium Oxybate Label § 5.3 (July 2016), [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/202090lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202090lbl.pdf) [<https://perma.cc/KM53-8HP4>].

<sup>311</sup> Sharp, *supra* note 240, at 10.

<sup>312</sup> See U.S. Patent Nos. 7,668,730 (filed Dec. 17, 2002); 7,765,107 (filed Apr. 1, 2005); 7,895,059 (filed Feb. 11, 2010); and 8,457,988 (Aug. 27, 2012). The first sentence of the abstract for each of the seven patents provides: “A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug.” *Id.*

~~patent, method, or process~~ for a license under which the applicant for such abbreviated new drug application may use an aspect of the elements to assure safe use, if required under subsection (f) for the applicable listed drug, that is ~~claimed by a patent that has not expired or is protected~~ by a method or process that as a trade secret is entitled to protection.<sup>313</sup>

#### E. REMS Patents as Prior Art

The final proposal borrows a strategy from the AIA, in which Congress deemed tax-strategy patents to fall within the “prior art.”<sup>314</sup> This uncodified amendment to section 102 provides:

For purposes of evaluating an invention under section 102 or 103 of title 35 . . . any strategy for reducing, avoiding, or deferring tax liability, whether known or unknown at the time of the invention or application for patent, shall be deemed insufficient to differentiate a claimed invention from the prior art.<sup>315</sup>

The concept of “[t]ax strategy can be as simple as a plan to buy tax-exempt bonds or invest in an IRA to reduce your tax liability or as complex as some sort of sale-leaseback tax shelter involving multiple domestic and foreign corporations and partnerships.”<sup>316</sup>

AIA section 14 renders tax-strategy patents invalid for lack of novelty under section 102 and for obviousness under section 103.<sup>317</sup> In other words, while the

<sup>313</sup> 21 U.S.C.A § 355-1(i)(1)(B)(ii) (West 2017). Trade secrets present less concern since they do not lead to claims based on induced infringement and do not block reverse engineering, allowing generics to replicate basic elements such as communicating and registering with pharmacies.

<sup>314</sup> Prior art is “information which is available or accessible to the public at the time of invention.” JOHN GLADSTONE MILLS III ET AL., PATENT LAW BASICS § 7:2, Westlaw (last updated Nov. 2016).

<sup>315</sup> Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 14(a), 125 Stat. 284, 327 (2011) [hereinafter AIA section 14]. The term “tax liability” refers to “any liability for a tax under any Federal, State, or local law, or law of any foreign jurisdiction, including any statute, rule, regulation, or ordinance that levies, imposes, or assesses such tax liability.” *Id.* § 14(b).

<sup>316</sup> 157 CONG. REC. S1198 (daily ed. Mar. 3, 2001) (statement of Sen. Grassley).

<sup>317</sup> The amendment did not ban patents outright under section 101 for two primary reasons. First, the statute sought to avoid “quadrupl[ing] the length of a foundational section of the patent code in order to address a relatively minor matter” by instead “ban[ning] tax-strategy patents using an uncodified amendment” to section 102. Joe Matal, *A Guide to the Legislative History of the America Invents Act: Part I of II*, 21 FED. CIR. B.J. 435, 502-03 (2012). Second, though the drafters were concerned with the impact of tax-strategy patents, a blanket prohibition under section 101 would have been challenged on the grounds that

[e]ven opponents of tax strategy patents agree that there are accounting or computerized data manipulation techniques with tax components that should be patentable (e.g., Turbo Tax or other tax preparation software), but they are adamant that tax planning strategies that represent the abstract ideas of tax planners applying interpretations of tax law to proposed transaction structures should not be.

AIA implicitly recognizes that tax-strategy patents could satisfy patentable subject matter,<sup>318</sup> any such finding under section 101 would succumb to the patent's obviousness and lack of novelty. The section provides exclusions for tax preparation and non-tax-strategy financial management.<sup>319</sup> But a claim that, for example, "explicitly recites deferring federal taxation of corporate profits" with "steps . . . disclosed for securing the tax deferral benefits taught" would be deemed a tax strategy "insufficient to differentiate from the prior art" under sections 102 and 103.<sup>320</sup>

The reason for the AIA's ban on tax-strategy patents is clear: the public must be allowed to comply with the law without risking infringement. Many drafters objected to such patents, with one representative lamenting that they were "outrageous" as "[n]o one should have to pay a royalty to pay their taxes" or "have sole ownership of how taxes are paid."<sup>321</sup> Similarly, another opined that "[t]ax strategies are bad because they allow the tax law to be patented" and "[a] tax strategy patent makes taxpayers choose between paying more than legally required in taxes or providing a windfall to a tax strategy patent-holder by paying a royalty to comply with the tax law."<sup>322</sup> Finally, the PTO has explained that the provision "aims to keep the ability to interpret the tax law and to implement such interpretation in the public domain, available to all taxpayers and their advisors."<sup>323</sup>

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Linda M. Beale, *Tax Patents: At the Crossroads of Tax and Patent Law*, 2008 U. ILL. J.L. TECH. & POL'Y, 117-18 (2008); *see also* 157 CONG. REC. S1202 (daily ed. Mar. 3, 2011) (statement of Sen. Grassley) ("[I]n order to allay the concerns of Intuit, makers of Turbo Tax, I have worked with Senator Baucus to make clear that tax preparation software such as Turbo Tax is not a tax strategy.").

<sup>318</sup> *Enfish, LLC v. Microsoft Corp.*, 56 F. Supp. 3d 1167, 1172 (C.D. Cal. 2014) ("[T]he America Invents Act mentions 'computer program product[s]' in a section discussing tax strategy patents. This section implicitly affirms software as eligible subject matter." (citation omitted)), *rev'd on other grounds*, 822 F.3d 1327 (Fed. Cir. 2016).

<sup>319</sup> *See* AIA section 14(c) (excluding creations used (1) "solely for preparing a tax or information return" or (2) "solely for financial management, to the extent that it . . . does not limit the use of any tax strategy"); *see also* Matal, *supra* note 317, at 504 (exclusions are "devoid of any substantive effect" and simply confirm that section 14's "ban on tax-strategy patents does not ban patenting things that are not tax strategies").

<sup>320</sup> *See* U.S. PATENT & TRADEMARK OFFICE, *Section 14—Tax Strategies Deemed to be Within the Prior Art Introductory Examples*, at 4, [https://www.uspto.gov/sites/default/files/aia\\_implementation/tax-strategies-training-examples.pdf](https://www.uspto.gov/sites/default/files/aia_implementation/tax-strategies-training-examples.pdf) [<https://perma.cc/X2R3-HVAK>] (last visited Sept. 17, 2017) (internal quotation marks omitted).

<sup>321</sup> 153 CONG. REC. H10,273 (daily ed. Sept. 7, 2007) (statement of Rep. Boucher).

<sup>322</sup> 157 CONG. REC. S1201 (daily ed. Mar. 3, 2001) (statement of Sen. Grassley).

<sup>323</sup> Memorandum from Robert W. Bahr, Acting Assoc. Comm'r for Patent Examination Pol'y, to Patent Examining Corps, at 1 (Sept. 20, 2011), [https://www.uspto.gov/sites/default/files/aia\\_implementation/tax-strategies-memo.pdf](https://www.uspto.gov/sites/default/files/aia_implementation/tax-strategies-memo.pdf) [<https://perma.cc/EJG7-P6XX>]; *see also* H.R. REP. NO. 112-98, pt. 1, at 51-52 (2011). The House Report on the AIA characterized the situation:

Just as tax-strategy patents cannot be used to bottleneck compliance with the law, REMS patents also should not be permitted to. In each case, a patent covers an obligation to comply with a government mandate. While tax-strategy patents may have a more widespread application, the case for treating REMS patents as prior art is stronger in some ways than the case for doing so for tax-strategy patents. The tax laws, for example, do not mandate that a corporation set up parent and subsidiary entities as a means of reducing tax burdens. Instead, such claims are merely drawn to a method of complying with the tax laws if a corporation *desires* to set up such a structure to manage tax obligations. In contrast, the FDA *mandates* the use of REMS, with the patenting of such programs creating a direct conflict with a government obligation. Put another way, a generic's infringement of a REMS patent results not from its decision to develop a strategy to evaluate and mitigate risk but from a regulatory requirement to ensure uniform risk management.

The remedy is simple. Congress can either amend AIA section 14 with a subsection, or adopt an entirely new section, adding the following language:

Any method or system approved by the FDA as a component of a Risk Evaluation and Mitigation Strategy (REMS), whether known or unknown at the time of the invention or application for patent, shall be deemed insufficient to differentiate a claimed invention from the prior art.

#### CONCLUSION

Patents often serve important purposes. But patents on REMS programs undermine the generic competition at the heart of crucial regulatory regimes. This Article has offered five proposals to address this problem. Delisting patents from the Orange Book would preclude brand firms from obtaining inappropriate 30-month stays. More rigorous challenges would prevent invalid patents from blocking generic competition. A rigorous application of *eBay* would result in damages rather than injunctions. And an amendment to the FDAAA or AIA would mitigate the most harmful effects of REMS patents. In short, the proposals offered in this Article promise to reconcile the conflict between REMS patents and generic competition.

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In recent years, the numbers of patents on tax strategies have increased. Critics assert that it is not fair to permit patents on techniques used to satisfy a government mandate, such as compliance with the Internal Revenue Code. Tax preparers, lawyers, and planners have a long history of sharing their knowledge regarding how to file returns, plan estates, and advise clients. The ability to interpret the tax law and implement such interpretations should remain in the public domain, available to all taxpayers and their advisors.

*Id.*