

REMS AS A COMPETITIVE TACTIC: IS BIG PHARMA HIJACKING DRUG ACCESS AND PATIENT SAFETY?

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ABSTRACT

Recent amendments to the Food, Drug, and Cosmetic Act give authority to the Food and Drug Administration (FDA) to require risk evaluation and mitigation strategies (REMS) either as a condition for new drug approval or for continued marketing and distribution of an existing drug. The goal of instituting REMS for particular products is to provide ongoing assurance that the benefits continue to outweigh the risks once a drug is on the market and in widespread use by consumers. REMS take many forms and may require a medication guide for patients; physician prescribing information; communications to health care providers and pharmacies; limitations on labeling, promotion, and prescribing to assure safe use by patients; and a detailed plan for REMS implementation. The FDA has since effectuated over 70 REMS programs for new and already-approved drug products, with over 30 of those REMS containing requirements setting limitations on distribution, access, and use.

While the implementation of REMS has strengthened the post market oversight of drug products, there is concern that pharmaceutical companies are defensively utilizing the statutory provisions to hinder generic competition. This article examines the competitive use of REMS by brand name pharmaceutical companies to inhibit generic drug competition, highlighting two rising practices: (1) the refusal to supply generic competitors with drug samples for use in bioequivalence testing citing REMS distribution restrictions; and (2) the assertion of patent rights over comprehensive patient treatment and delivery methods contained in FDA-

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REMS AS A COMPETITIVE TACTIC: IS BIG PHARMA HIJACKING DRUG ACCESS AND PATIENT SAFETY?

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I. INTRODUCTION

The pharmaceutical industry has long-been criticized for its use of anticompetitive tactics. Brand pharmaceutical companies have been publicly accused of several activities to increase profits and stifle competition. These include shifting demand to a modified form of an existing brand drug (often called “product hopping”),¹ using authorized generics² to retain market share, frivolously filing citizens petitions to delay generic market entry,³ and using reverse payment settlements to keep generic drugs off the market during their 180 day exclusivity period (otherwise known as pay-for-delay settlements).⁴ A persistent opponent in these tactics, the Federal Trade Commission (FTC) routinely invokes antitrust and unfair competition law to frame legal challenges. In fact, the 2013 Supreme Court case *Federal*

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¹ See generally, M. Sean Royall, *Antitrust Scrutiny of Pharmaceutical ‘Product Hopping’*, 28(1) ANTITRUST 71-77 (Fall 2013).

² FED. TRADE COMM’N, AUTHORIZED GENERIC DRUGS: SHORT-TERM EFFECTS AND LONG-TERM IMPACT (Aug. 2011). [*Hereinafter* F.T.C., AUTHORIZED GENERIC DRUGS]

³ Matthew Avery, William Newsom, and Brian Hahn, *The Antitrust Implications of Filing ‘Sham’ Citizens Petitions with the Food and Drug Administration*, 65 HASTINGS L.J. 113, 113-152 (2013).

⁴ See FED. TRADE COMM’N, PAY-FOR-DELAY: WHEN DRUG COMPANIES AGREE NOT TO COMPETE (last visited July 18, 2015) available at <https://www.ftc.gov/news-events/media-resources/mergers-competition/pay-delay>. [*Hereinafter* F.T.C., PAY-FOR-DELAY]

Trade Commission v. Actavis examined pay-for-delay settlements entered into between new drug application (NDA) patent holders and generic applicants, holding that the settlement agreements were not *per se* illegal but subject to a rule-of-reason analysis.⁵

Many are now pointing to brand pharmaceutical manufacturers use of Risk Evaluation and Mitigation Strategies (REMS) as the latest anticompetitive tactic. The Food and Drug Administration Amendments Act of 2007 (FDAAA)⁶ introduced REMS to enhance the post-approval authority over drugs by the Food and Drug Administration (FDA). FDAAA also contains new statutory provisions that allow the FDA to require further studies for safety and efficacy, along with increased authority for the FDA to review these commitments on a continuing basis.⁷ The FDA can require REMS as either a condition of approval⁸ or, in the case of already approved products, as a subsequent condition for continued marketing.⁹ REMS may require a medication guide for patients; physician prescribing information; communications to health care providers and pharmacies; limitations on labeling, promotion, and prescribing in order to assure safe use by patients; and a plan for implementation.¹⁰ Violations of the statute trigger civil money penalties and subject manufacturers to litigation under misbranding provisions within the Food, Drug and Cosmetic Act (FDCA).¹¹ To date, the FDA has implemented over 70 REMS, roughly half of which

⁵ F.T.C. v. Actavis, 133 S. Ct. 2223 (2013). Since the Supreme Court's decision, several additional cases have arisen questioning the scope of pay-for-delay settlements. For example, the FTC has filed suit against AbbVie and Teva Pharmaceuticals in the Eastern District of Pennsylvania for preventing generic versions of the brand drug AndroGel, a topical drug indicated for men with low testosterone, from entering the market. See Diane Bartz, *AbbVie, Teva Broke Law in AndroGel 'Pay for Delay' Deal, U.S. FTC Says*, REUTERS, Sept. 8, 2014, available at <http://www.reuters.com/article/2014/09/08/abbvie-teva-pharm-ind-antitrust-idUSL1N0R91A520140908>; Peter Frost, *AbbVie Sued by FTC for Paying to Delay Generic Drug*, CHICAGO TRIBUNE, Sept. 8, 2014, available at <http://www.chicagotribune.com/business/breaking/chi-abbvie-lawsuit-delay-generic-androGel-20140908-story.html>.

⁶ Pub. L. 110-85 (2007), codified in scattered sections of 21 U.S.C.

⁷ FDCA §§ 505(p), 505-1 (2014)/21 U.S.C. §§ 355(p), 355-1 (2014).

⁸ FDCA § 505-1(a)(1)/21 U.S.C. § 355-1(a)(1).

⁹ FDCA § 505-1(a)(2)/21 U.S.C. § 355-1(a)(2).

¹⁰ FDCA § 505-1(c)-(f)/21 U.S.C. § 355-1(c)-(f).

¹¹ FDCA § 502(y)/21 U.S.C. § 352(y).

include elements to assure safe use (ETASU) that often take the form of distribution restrictions, training and recordkeeping requirements for prescribers and pharmacists, and prescribing limitations.¹²

These ETASU REMS are now being utilized by the pharmaceutical industry to erect hurdles for generic drug applicants attempting to enter the market. A July 2014 study estimates that \$5.4 billion per year has been lost in prescription drug savings due to distribution restrictions imposed by brand drug manufacturers under the auspices of REMS requirements.¹³ Brand manufacturers subject to REMS for an NDA drug product claim that they cannot make samples of that drug available to the generic applicant because they would be in violation of distribution restrictions placed on the products by the FDA in the REMS. However, to obtain FDA approval through the generic drug approval process, a generic applicant must show bioequivalence to the reference NDA product through pharmacokinetic and pharmacodynamic measures.¹⁴ In order to demonstrate this bioequivalence, the generic applicant must have access to the reference drug to conduct appropriate studies.

The medical community is already targeting this practice as problematic for the U.S. healthcare system and for individual patients, noting that it is a direct threat to the effective use of a drug-safety tool in order to increase profits and keep generic products off the market. In an April 2014 *NEW ENGLAND JOURNAL OF MEDICINE* article, the physician authors urge that “the use of REMS requirements to block the market entry of generic drugs could well lead to higher health care costs and adverse patient outcomes.”¹⁵

The controversial tactic is already playing out in court in New Jersey. Mylan Pharmaceuticals filed a complaint earlier this year against Celgene Corporation, claiming violations of federal antitrust

¹² See FOOD AND DRUG ADMIN., APPROVED RISK EVALUATION AND MITIGATION STRATEGIES (REMS), available at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>. [Hereinafter F.D.A., APPROVED REMS]

¹³ ALEX BRILL, MATRIX GLOBAL ADVISORS, *Lost Prescription Drug Savings from Use of REMS Programs to Delay Generic Market Entry*, GENERIC PHARM. ASS'N (July 2014), http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf.

¹⁴ FDCA § 505(j)(2)(iv)/21 U.S.C. § 355(j)(2)(iv).

¹⁵ Ameet Sarpatwari, Jerry Avorn, and Aaron S. Kesselheim, *Using a Drug-Safety Tool to Prevent Competition*, 370 N. ENGL. J. MED. 1476, 1476-1478 (2014).

law.¹⁶ Mylan alleges that Celgene refuses to distribute the products Thalomid (thalidomide) and Revlimid (lenalidomide) for bioequivalence testing for products in development by Mylan.¹⁷ Because of their teratogenic nature, the FDA has invoked REMS for both Thalomid¹⁸ and Revlimid¹⁹ consisting of various extensive requirements in the form of ETASU to prevent embryo-fetal exposure, among other things. One core aspect of the ETASU is strong oversight and requirements for distribution only through authorized dispensing pharmacies.²⁰ Celgene's position is that the distribution restrictions prohibit the transfer of drug samples to Mylan for any purpose, including bioequivalence studies.²¹

The FTC has taken a strong interest in the case, and filed an amicus brief on June 17, 2014.²² In the brief, the FTC argues that Celgene is potentially engaging in exclusionary conduct in violation of the Sherman Act for its "refusal to sell to rivals."²³ The FTC notes that Celgene may be in violation of both Section 1 and 2 of the Sherman Act by not only refusing to directly provide samples to Mylan, but also implementing restrictions that prevent Mylan from purchasing samples through customary distribution channels.²⁴ Celgene moved to dismiss.²⁵ In a December 22, 2014 decision, Judge Salas of the U.S. District Court of New Jersey denied

¹⁶ Original Complaint, Mylan Pharms. Inc. v. Celgene Corp., No. 14-2094 (D.N.J. Apr. 3, 2014).

¹⁷ *Id.* at 4.

¹⁸ FOOD AND DRUG ADMIN., Thalomid (thalidomide) REMS, NDA # 020785 (Initial REMS Approved Aug. 2010; Most Recent Modification Nov. 2013), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM222649.pdf>. [*Hereinafter* Thalomid REMS].

¹⁹ FOOD AND DRUG ADMIN., Revlimid (lenalidomide) REMS, NDA # 021880 (Initial REMS Approved Aug. 2010; Most Recent Modification Nov. 2013), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM222644.pdf> [*Hereinafter* Revlimid REMS].

²⁰ Thalomid REMS, *supra* note 18.

²¹ See Mylan, *supra* note 16.

²² Brief for Fed. Trade Comm'n as Amicus Curiae, Mylan Pharm. Inc. v. Celgene Corp., No. 14-2094 (D.N.J. June 17, 2014).

²³ *Id.* at 8.

²⁴ *Id.* at 1-2.

²⁵ *Id.* at 1.

Celgene's motion to dismiss claims regarding Section 2 and dismissed Mylan's allegations under Section 1.²⁶ Celgene appealed and the Third Circuit rejected their request for immediate review in March 2015.²⁷ This litigation is being closely monitored by industry, as it has the potential to be the first case to assess the merits; previous cases alleging antitrust violations for similar activity have resulted in settlement agreements.²⁸

This article examines the use of REMS by pharmaceutical companies to inhibit generic drug competition, highlighting two rising practices: (1) refusal to supply generic competitors with drug samples for use in bioequivalence testing citing REMS restrictions; and (2) assertion of patent rights over patient treatment and delivery methods contained in FDA-approved REMS. The article offers several approaches to address these current concerns.

II. COMPETITION, ANTITRUST, AND BIG PHARMA

A. A Brief History

The FDA and its predecessor governmental units have long-served as the gatekeeper to the nation's drug supply. The first Pure Food and Drug Act in 1906 created obligations for drug manufacturers based on concepts of adulteration and misbranding. The 1906 Act paved the way for successive amendments and refinement of the drug approval system, adding the now touchstone concepts of safety and efficacy achieved through clinical trials, establishing rigorous pre-and post-market requirements for drug sponsors and manufacturers, and providing hefty administrative and enforcement powers to the FDA. In 1984, Congress enacted the Drug Price Competition and Patent Term Extension Act,²⁹ otherwise known

²⁶ Order on Motion to Dismiss, *Mylan Pharms. Inc. v. Celgene Corp.*, No. 14-2094, (D.N.J. Dec. 23, 2014).

²⁷ Vin Gurreri, *3rd Circ. Declines to Hear Mylan, Celgene Antitrust Fight*, LAW360 (Mar. 6, 2015), <http://www.law360.com/articles/628588/3rd-circ-declines-to-hear-mylan-celgene-antitrust-fight>.

²⁸ See *Actelion Pharms., Ltd. v. Apotex Inc.*, No. 12-5743 (D.N.J. 2012); *Lannett Corp., Inc. v. Celgene Corp.*, No. 08-3920 (E.D. Pa. 2011).

²⁹ Pub. L. 98-417 (1984).

as the Hatch-Waxman Act,³⁰ as a means to both incentivize generic drug innovation (thereby reducing drug costs) and support legitimate patent rights for new drug sponsors. To accomplish this, the legislation created the abbreviated new drug application (ANDA) and approval process.

The ANDA process, colloquially known as the generic drug approval process, involves two key aspects critical to discussions of drug competition and market behavior. First, the legislation sets forth requirements for an ANDA product application to the FDA. These requirements are based on comparisons to the already-approved new drug, or “listed drug.”³¹ An ANDA applicant must generally show that the conditions of use for the generic drug have been previously approved for a reference listed drug (RLD);³² the route of administration, dosage form, and strength of the generic are the same as the listed drug;³³ the generic is bioequivalent to the listed drug;³⁴ and the proposed labeling is the same as that approved for the listed drug.³⁵ As will be discussed later in this article, the statutory requirements of the same labeling³⁶ and a showing of bioequivalence to the RLD are at the heart of recent anticompetitive tactics by brand name pharmaceutical manufacturers.

³⁰ See *id.* The legislation was introduced by Representative Orrin Hatch (R-Utah) and Senator Henry Waxman (D-CA). *Id.*

³¹ The already-approved new drug is referred to as the reference listed drug (RLD) because the new drug is listed in the Orange Book, otherwise known as the APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, Drug Approvals and Databases, U.S. FOOD AND DRUG ADMIN. (last updated Feb. 17, 2015), <http://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>. The Orange Book is published and maintained by the FDA. *Id.* Listed drugs are to be used as the reference point for bioequivalence measures by the generic drug sponsor. *Id.* The Orange Book also contains patents disclosed by the listed drug sponsors, as required by the statute. *Id.*

³² 21 U.S.C. § 355(j)(A)(i) (2012).

³³ *Id.* § 355(j)(A)(iii). Any variation may be the subject of a petition to the FDA. *Id.*

³⁴ *Id.* § 355(j)(A)(iv). If subject to a petition as described above, the applicant must demonstrate that the active ingredient of the generic are of the same pharmacological or therapeutic class and expected to have the same therapeutic effect. *Id.*

³⁵ *Id.* §355(j)(A)(v). Changes to the label of a listed drug may be required for a generic if there are differences approved by the FDA in a petition or because of production or distribution differences. *Id.*

³⁶ REMS are subject to the misbranding provisions of the statute and FDA regulations. Concepts of misbranding deal generally with violations of labeling requirements. 21 U.S.C. §352(y) (2012).

The second key aspect of the legislation is that it sets forth a multi-choice patent certification procedure for all ANDA applicants. Each generic applicant must certify one of four conditions: (I) a patent for the listed drug has not been filed;³⁷ (II) the existing patent on the listed drug has expired;³⁸ (III) the specific date on which a patent for a listed drug will expire;³⁹ or (IV) the patent for the listed drug is invalid or will not be infringed by the generic manufacture, use, or sale of the generic drug.⁴⁰ The last option is called a “Paragraph IV certification” and often triggers infringement litigation between a patented listed drug manufacturer and the generic drug sponsor. Once a generic sponsor has filed such a certification with both the FDA and the RLD manufacturer, the RLD manufacturer can either file an infringement action against the generic drug sponsor or decide not to contest it. The statute provides intricate notice and timing elements for both parties,⁴¹ including a 30-month stay of any generic approval in the event of litigation.⁴² The first successful paragraph IV applicant is awarded 180-days of exclusivity on the market.⁴³

This litigation-forcing feature is the focal point of the Hatch-Waxman Act: generic drug manufacturers are essentially challenging the legal validity of existing patents by filing a paragraph IV certification. The goal of Congress was to foster this type of litigation in order to eliminate bad patents, enable lower-cost generic drugs to reach the market, and reduce the overall cost of prescription drugs to the health care system. This lofty goal has been achieved; the Generic Pharmaceutical Association found that between 2003 and 2012, generic drugs saved the U.S. health care system \$1.2 trillion.⁴⁴ Federal

³⁷ 21 U.S.C. § 355(j)(A)(vii)(I).

³⁸ *Id.* § 355(j)(A)(vii)(II).

³⁹ *Id.* § 355(j)(A)(vii)(III).

⁴⁰ *Id.* § 355(j)(A)(vii)(IV).

⁴¹ *Id.* §§ 355(j)(2)(B), (C).

⁴² *Id.* § 355(j)(5)(B)(iii).

⁴³ *Id.* § 355(j)(5)(B)(iv). This exclusivity is subject to limitations, including delay to enter the market. *Id.*

⁴⁴ GENERIC PHARM. ASS'N, *Generic Drug Savings in the U.S.*, <http://www.gphaonline.org/>, (2013), http://www.gphaonline.org/media/cms/2013_Savings_Study_12.19.2013_FINAL.pdf.

sources report that the first generic drug to enter the market typically offers a price 25% lower than that of the reference drug, rising to 80% cost savings with multiple generics on the market.⁴⁵

The brand name pharmaceutical market has responded with a variety of creative tactics to lessen the blow of generic competition. Several of these tactics have garnered attention in the legal and policy literature as being anticompetitive in nature and antithetical to antitrust law (if not in letter, in spirit). One tactic is shifting the demand for a brand drug that is soon to go off-patent to a modified form of an existing brand drug that has a longer patent term, often called “product hopping” or “forced switch.”⁴⁶ An article in the ARCHIVES OF INTERNAL MEDICINE reports that such a move by Abbott a few years ago with its cholesterol drug TriCor cost the U.S. health care system approximately \$700 million a year.⁴⁷ In September 2014, the attorney general of New York filed an antitrust lawsuit alleging that Actavis and its subsidiary Forest Laboratories are strong-arming physicians of Alzheimer’s patients to switch prescribing from the tablet formulation of the drug, Namenda immediate release (IR), to the extended-release capsules marketed as Namenda XR, which has a longer remaining patent life.⁴⁸ Judge Sweet of the Federal District Court of Manhattan issued a preliminary injunction in mid-December 2014 blocking Actavis from discontinuing sales of the older tablet formulation pending the decision in the case.⁴⁹ Actavis appealed the ruling⁵⁰ and the Second Circuit agreed to an expedited hearing of the appeal in early January 2015 but declined to stay the injunction

⁴⁵ FED. TRADE COMM’N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, 5 (June 2009), *available at* <https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf>.

⁴⁶ Royall, *supra note 1*.

⁴⁷ Nicholas Downing, et al., *Avoidance of Generic Competition by Abbott Laboratories’ Fenofibrate Franchise*, 172 ANN. INTERN. MED. 724, 724 (2012).

⁴⁸ Original Complaint, *State of New York v. Actavis Plc*, 1:14-cv-07473 (S.D.N.Y. Sept. 15, 2014); Andrew Pollack, *New York Files an Antitrust Suit Against the Maker of An Alzheimer’s Drug*, N.Y. TIMES, Sept. 16, 2014, at B3.

⁴⁹ Andrew Pollack, *Judge Rules Drug Maker Can’t Shelve Old Pill*, N.Y. TIMES, Dec. 12, 2014, at B6.

⁵⁰ *Id.*

during the interim.⁵¹

Another brand name tactic is designating authorized generics⁵² in order to retain market share, by entering into an agreement with another manufacturer to produce the same product but market it as a generic drug at a lower cost rather than as the brand name drug. This results in proceeds for the RLD drug manufacturer from both markets simultaneously. Yet another tactic is the frivolous filing of citizen petitions to delay generic market entry of generic drugs, causing the FDA to delay approval decisions and assess the merits of the citizen petitions.⁵³ The most highly-controversial tactic is, of course, the use of reverse payment settlements (otherwise known as pay-for-delay agreements) to keep generic drug of the market during their 180 day exclusivity period.⁵⁴ These settlements are discussed immediately below.

B. Reverse Settlement Agreements at the Supreme Court

Reverse settlement agreements have been the subject of debate and contention in the pharmaceutical industry for decades. They are named to reflect the nature of the agreement: the brand name manufacturer enters into an agreement with the would-be first generic drug applicant and ultimately pays the generic applicant to stay off the market for a specific period of time. Such an agreement is entered into in lieu of a litigation outcome. The payments are “reverse” in that the patent holder is paying the potential or alleged patent infringer. They are also termed “pay for delay” because they pay the generic to delay market entry of a legitimate, FDA-approved product.

Such lawsuits are based on the Federal Trade Commission Act (FTC Act), as well as the Sherman Antitrust Act. As described by the FTC, every case invoking the FTC Act also involves theories laid out

⁵¹ Kurt Orzeck, *2nd Cir. Oks Quick Actavis Appeal in Namenda Antitrust Suit*, LAW360 (Jan. 6, 2015), <http://www.law360.com/articles/608825/2nd-circ-oks-quick-actavis-appeal-in-namenda-antitrust-suit>.

⁵² FED. TRADE COMM'N, AUTHORIZED GENERIC DRUGS, *supra* note 2.

⁵³ Avery, Newsom, and Hahn, *supra* note 3. A recent addition to the statute permits the FDA to reject any application where the clear intent is to delay the entry of a competitor. 21 U.S.C. § 355(q)(1)(E).

⁵⁴ See FED. TRADE COMM'N, PAY-FOR-DELAY, *supra* note 4.

in the Sherman Act:

The Federal Trade Commission Act bans “unfair methods of competition” and “unfair or deceptive acts or practices.” The Supreme Court has said that all violations of the Sherman Act also violate the FTC Act. Thus, although the FTC does not technically enforce the Sherman Act, it can bring cases under the FTC Act against the same kinds of activities that violate the Sherman Act. The FTC Act also reaches other practices that harm competition, but that may not fit neatly into categories of conduct formally prohibited by the Sherman Act. Only the FTC brings cases under the FTC Act.⁵⁵

The FTC relies on several statutory provisions in reverse settlement litigation. The provision of the FTC Act cited in reverse settlement cases, Section 5, provides that unfair methods of competition and unfair or deceptive acts or practices are illegal.⁵⁶ Section 1 of the Sherman Act provides that contracts in restraint of trade are illegal and deemed a felony, with a penalty of up to \$100,000,000 (corporation) or \$1,000,000 (individual), or by imprisonment not to exceed 10 years.⁵⁷ Section 2 provides that attempts to monopolize trade or commerce are also deemed a felony and punishable in the same manner as Section 1.⁵⁸

The legality of such settlements eventually made its way to the Supreme Court after an accumulation of lower court decisions. The Third, Sixth, and D.C. Circuits had all determined that strict antitrust law should apply to reverse settlements, while the Second, Eleventh, and Federal Circuits had applied a test analyzing the scope of the patent, leading to an increased likelihood of such settlements being upheld. On the one side of the issue, the Sixth Circuit held such reverse settlements are *per se* illegal in the pharmaceutical context⁵⁹; the Third Circuit applied a quick look analysis, holding that any settlement that had the effect of delaying market entry of a generic was *prima facie* evidence of an unreasonable restraint on trade.⁶⁰ In

⁵⁵ FED. TRADE COMM'N, THE ANTITRUST LAWS, available at <http://www.ftc.gov/tips-advice/competition-guidance/guide-antitrust-laws/antitrust-laws> (last visited June 17, 2015).

⁵⁶ 15 U.S.C. § 45(a)(2014).

⁵⁷ 15 U.S.C. § 1 (2014).

⁵⁸ 15 U.S.C. § 2 (2014).

⁵⁹ *In re Cardizem CD*, 33 F.3d 896, 915 (6th Cir. 2003).

⁶⁰ *In re K-Dur*, 686 F.3d 197, 218 (3rd Cir. 2012).

contrast, both the Second Circuit⁶¹ and the Eleventh Circuit⁶² utilized a scope of the patent analysis, where such settlements were to be upheld as lawful unless the terms expanded the scope of the lawfully-obtained patent.⁶³

The decision of the Eleventh Circuit made its way to the Supreme Court in *Federal Trade Commission v. Actavis*.⁶⁴ There, the Supreme Court rejected the lower court's application of the scope of the patent (as well as the FTC's quick look analysis), holding that the FTC should have been given the opportunity to prove its claim, applying instead a rule-of-reason analysis.⁶⁵ The rule of reason analysis posits that the likelihood of the reverse settlement bringing about anticompetitive effects depends on its size, its scale in relation to future litigation costs, its independence from other services that might represent payment, and the lack of any other convincing justification.⁶⁶ The Court arrived at this decision based on five considerations. First, the restraint at issue has the "potential for genuine adverse effects on competition."⁶⁷ Second, the "anticompetitive consequences will at least sometimes prove unjustified."⁶⁸ Third, "where a reverse payment threatens to work unjustified anticompetitive harm, the patentee likely possesses the power to bring that harm about in practice."⁶⁹ Fourth, an action based in antitrust law "is likely to prove more feasible administratively than the Eleventh Circuit believed."⁷⁰ Fifth "the fact that a large, unjustified reverse payment risks antitrust liability does not prevent litigating parties from settling their lawsuit."⁷¹ Taken together, the

⁶¹ *In re Tamoxifen Citrate*, 466 F.3d 187, 193 (2nd Cir. 2006).

⁶² *F.T.C. v. Watson Pharms.*, 677 F.3d 1298 (3rd Cir. 2012), *rev'd* by *F.T.C. v. Actavis*, 133 S. Ct. 2223 (2013).

⁶³ *Id.*

⁶⁴ *F.T.C. v. Actavis*, 133 S. Ct. 2223 (2013).

⁶⁵ *Id.*

⁶⁶ *Id.* at 2237.

⁶⁷ *Id.* at 2234.

⁶⁸ *Id.* at 2235.

⁶⁹ *Id.* at 2236.

⁷⁰ *Id.*

⁷¹ *Id.* at 2237.

Court found that the desirability of settlements and the application of “near-automatic antitrust immunity” by the Eleventh Circuit were outweighed by these five considerations.⁷²

The Supreme Court’s decision has not resolved the pay-for-delay issue. In fact, the FTC recently released a report aggregating branded drug firm settlements with generic competitors for fiscal year 2013.⁷³ Of 145 final settlements in 2013, 29 were categorized as creating potential pay-for-delay agreements because they involved marketing restrictions for a set time on the generic manufacturer coupled with compensation from the brand manufacturer.⁷⁴ Although down from 40 such agreements in 2012, these numbers are similar to FTC data gathered from the years 2010 and 2011.⁷⁵ The FTC also filed the reportedly first pay-for-delay case since *Actavis* in the Eastern District of Pennsylvania in September 2014. The litigation names AbbVie Inc. and others, alleging violations of Section 5 of the FTC Act, for “entering into an agreement to maintain a monopoly over and restrain generic competition.”⁷⁶ Sources report that the complaint “represents a departure from the FTC’s approach in these cases in that it alleges that the underlying patent infringement litigation was baseless and motivated by anti-competitive purposes.”⁷⁷ Due to the scope of the Court’s decision in *Actavis* leaving the structure of the rule-of-reason analysis to the lower courts, these challenges from the FTC will likely continue in many variations.

While continuing to police reverse settlements by pharmaceutical companies, the FTC has also begun to invest resources investigating potential FTC Act violations through use of REMS.

⁷² *Id.*

⁷³ FED. TRADE COMM’N, BUREAU OF COMPETITION, AGREEMENTS FILED WITH THE FEDERAL TRADE COMMISSION UNDER THE MEDICARE PRESCRIPTION DRUG IMPROVEMENT AND MODERNIZATION ACT OF 2003, *available at* <http://www.ftc.gov/system/files/documents/reports/agreements-filled-federal-trade-commission-under-medicare-prescription-drug-improvement/141222mmafy13rpt.pdf>.

⁷⁴ *Id.* at 1.

⁷⁵ *Id.* at 2.

⁷⁶ Paul M. Eckles, et al, *What FTC Is Saying In 1st Post-Actavis Pay-For-Delay Case*, LAW 360 (Sept. 11, 2014), <http://www.law360.com/articles/576140/what-ftc-is-saying-in-1st-post-actavis-pay-for-delay-case>.

⁷⁷ *Id.*

III. RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

A. The Statute

Prior to the enactment of FDAAA in 2007, the FDA employed a piecemeal approach to imposing certain restrictions on access, use, and distribution of approved drug products. Generally, any approved drug product that raised particular safety risks because of route of administration, dosage, contraindications, patient population, or other factors could be subjected to FDA restrictions in any number of forms. However, the FDA was limited in pursuing such violations and attempted to enforce those restrictions using either the general misbranding provisions⁷⁸ or the new drug approval provisions under the FDCA.⁷⁹ Given the lack of express enforcement authority for post-market obligations, enhancement of the statutory framework for post-market oversight was actively contemplated in Congress for years. The result was FDAAA.

With FDAAA, Congress established explicit, unified statutory provisions regarding requirements to evaluate and mitigate the risks of particular products through what the statute called risk evaluation and mitigation strategies, or REMS.⁸⁰ The goal was to provide FDA with the mechanism to assure that the benefits continued to outweigh the risks of the product once it was on the market. REMS, first officially implemented in 2008, significantly enhanced the FDA's post-market authority and included a wide range of risk management tools designed to manage known or potential serious risks associated with an approved drug. The FDA has required REMS in approximately 40% of all NDAs.⁸¹ For drugs already on the market, the FDA may require REMS when it becomes aware of new safety information about serious risks associated with a product. Applicants are initially responsible for developing the substance of REMS when required by the FDA, and the REMS are subject to FDA refinement and agreement prior to implementation.

REMS come in many forms: they can require lab tests prior to

⁷⁸ FDCA § 502/21 U.S.C. §352 (2013).

⁷⁹ FDCA § 505/21 U.S.C. §355 (2013).

⁸⁰ FDCA §§ 505(p), 505-1/21 U.S.C. §§ 355(p), 355-1. (2013).

⁸¹ Brill, *supra* note 13, at 1.

product usage; limitations on who may prescribe or what pharmacies may distribute a particular drug; the creation of patient registries to facilitate tracking; additional informed consent requirements; a Medication Guide for patients; physician prescribing information; implementation plans; communications to health care providers and pharmacies; and various limitations on labeling, promotion, and prescribing to assure safe use.⁸² FDAAA gave the FDA significant enforcement mechanisms for violations of REMs, which are deemed to be misbranding violations⁸³ and carry additional civil money penalties.⁸⁴

For approved drugs with known serious risks based on inherent toxicity or potential harmfulness, the FDA may require REMS to assure safe clinical use of the drug.⁸⁵ Formerly established through what were called restricted distribution programs, these specific REMS mechanisms are now called elements to assure safe use (ETASU) under the statute. The statute provides multiple ways in which the FDA can structure these ETASU:

The elements to assure safe use . . . shall include 1 or more goals to mitigate a specific serious risk listed in the labeling of the drug and, to mitigate such risk, may require that—

(A) health care providers who prescribe the drug have particular training or experience, or are specially certified (the opportunity to obtain such training or certification with respect to the drug shall be available to any willing provider from a frontier area in a widely available training or certification method (including an on-line course or via mail) as approved by the Secretary at reasonable cost to the provider);

(B) pharmacies, practitioners, or health care settings that dispense the drug are specially certified (the opportunity to obtain such certification shall be available to any willing provider from a frontier area);

(C) the drug be dispensed to patients only in certain health care settings, such as hospitals;

(D) the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results;

⁸² See FDCA § 505-1/21 U.S.C. § 355-1 (2013).

⁸³ FDCA § 502/21 U.S.C. § 352 (2013).

⁸⁴ FDCA § 303(f)(4)(A)/21 U.S.C. § 333(f)(4)(A) (2013).

⁸⁵ FDCA § 505-1(f)(1)/21 U.S.C. §355-1(f)(1) (2013).

- (E) each patient using the drug be subject to certain monitoring; or
- (F) each patient using the drug be enrolled in a registry.⁸⁶

If an innovator RLD requires REMS, the generic drug entering the market based on measures of bioequivalence to that RLD must also adhere to the REMS as a function of the drug's required labeling. However, the statute establishing REMS also provides discretion to the Secretary (and ultimately through internal agency delegation to the Commissioner of the FDA) to waive requirements for a single, shared REMS system between a RLD and a generic drug.⁸⁷ Specifically:

A drug that is the subject of an [ANDA] and the listed drug shall use a single, shared system []. The Secretary may waive the requirement . . . for a drug that is the subject of an [ANDA], and permit the applicant to use a different, comparable aspect of the [ETASU] if the Secretary determines that – (i) the burden . . . outweighs the benefit . . ., taking into consideration the impact on health care providers, patients, the applicant, and the holder [of the RLD]; or (ii) An aspect of the [ETASU] 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 [ANDA] applicant certified that it has sought a license for use of an aspect of the [ETASU]. . . and it was unable to obtain a license.⁸⁸

This provision gives latitude to the Secretary of the DHHS (and thus the FDA Commissioner) to waive the requirement for a single, shared REMS system and allow a different, yet comparable aspect, either where the burden outweighs the benefit, or where a relevant part of the RLD REMS is the subject of a valid patent and the generic was unable to obtain a license. However, the ANDA applicant must certify that it sought a license from the reference product, and was unable to obtain such a license. The statute does not explain how this certification is to be satisfied, nor does it elaborate on what constitutes an inability to obtain a license.

However, the FDA has provided some direction on how an applicant may acquire permission to use a different, comparable aspect of the REMS. The FDA recently published draft guidance for

⁸⁶ FDCA §505-1(f)(3)/21 U.S.C. §355-1(f)(3) (2013).

⁸⁷ 21 U.S.C. §355-1(i)(1)(B) (2013).

⁸⁸ *Id.*

industry regarding procedures to receive documentation from the agency that the bioequivalence study protocols contain safety protections comparable to the REMS for the RLD.⁸⁹ The guidance is relatively straightforward: the prospective ANDA applicant is to check the FDA online listing of approved REMS to identify applicable REMS for the RLD; prepare bioequivalence protocols incorporating necessary elements of the RLD's labeling and ETASU in order to perform the study or studies in a safe manner; and submit the draft protocols, informed consent documents, and informational materials involved in the study or studies to the Office of Generic Drugs (OGD) by email. On review, the OGD's Office of Bioequivalence through the Division of Bioequivalence and Division of Clinical Review identify any concerns and communicate via letter to the ANDA applicant recommended changes.⁹⁰ Upon revision by the applicant, the FDA will review the changes and either issue a determination letter advising the applicant of the agency's acceptance of the protocols or request additional changes.⁹¹ When the applicant makes a request, the FDA will send the RLD sponsor a letter reporting their determination of the comparability of protocols for REMS purposes.⁹² Additionally, the FDA will inform the RLD that the "FDA will not consider it a violation of REMS for the RLD sponsor to provide the designated potential ANDA applicant (or its agent) a sufficient quality of drug product to allow it to perform the testing necessary to support its ANDA and otherwise meet the requirements for ANDA approval."⁹³ While this language serves to confer enforcement discretion on the part of the agency allowing the RLD to supply the drug product to the ANDA applicant, it does not affirmatively require the RLD sponsor to supply the drug product.

Notably, the statute also contains a limitation that seemingly

⁸⁹ FOOD AND DRUG ADMIN., DRAFT GUIDANCE: HOW TO OBTAIN A LETTER FROM FDA STATING THAT BIOEQUIVALENCE STUDY PROTOCOLS CONTAIN SAFETY PROTECTIONS COMPARABLE TO APPLICABLE REMS FOR RLD (Dec. 2014), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425662.pdf>. [*Hereinafter* FDA DRAFT GUIDANCE: HOW TO OBTAIN A LETTER]

⁹⁰ *Id.* at 3.

⁹¹ *Id.* at 3-4.

⁹² *Id.* at 4.

⁹³ *Id.*

relates to the issue of a refusal to supply, though it does not expressly state its scope:

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 section 355(b)(2) or (j) of this title or to prevent application of such element under subsection (i)(1)(B) to a drug that is the subject of an abbreviated new drug application.⁹⁴

The language of this limitation provides a mandatory requirement that “no holder of an approved covered application shall use any element to assure safe use. . .to block or delay approval.”⁹⁵ However, the statute does not construe the type of conduct that is considered to block or delay, nor does it include penalties for violations. A bill introduced in Congress in September 2014 seeks to remedy this issue, by mandating the Secretary to require that the RLD “not adopt, impose, or enforce any condition relating to the sale, resale, or distribution of the covered product, including any condition adopted, imposed, or enforced as an aspect of a [REMS] approved by the Secretary, that restricts or has the effect of restricting the supply of such covered product to an eligible product developer for development or testing purposes.”⁹⁶ The bill refers to “commercially reasonable, market-based prices” as a measure for RLD sponsors, signaling the ability to charge for such products within commercially reasonable terms.⁹⁷ The bill provides for enforcement by the FDA as a violation of REMS, as well as private enforcement and remedies of injunctive relief and treble damages under the Clayton Act.⁹⁸

The terms and scope of the statutory provisions have yet to be construed by the FDA or the courts. As discussed in Part IV, generic pharmaceutical companies have petitioned the FDA for guidance and action on the matter in the wake of resistance from the brand name companies to share REMS elements. It is unclear whether the FDA is obligated to facilitate collaboration between the generic and brand

⁹⁴ 21 U.S.C. § 355-1(f)(8).

⁹⁵ *Id.*

⁹⁶ Fair Access for Safe and Timely Generics Act of 2014, H.R. 5657, 113th Congr., at § 3(a).

⁹⁷ *Id.*

⁹⁸ *Id.*

drug manufacturer; the effect of a failure of a brand manufacturer to share such information for use as part of a single, shared REMS system; or whether and what type of authority the FDA or the courts have to enforce the limitation in the statute regarding the “block[ing] or delay of approval.”⁹⁹ The FDA has thus far declined to take a position on any of these issues. Reasons for the FDA’s reluctance may be based on other factors, including more pressing agency priorities, current fiscal conditions, the pending legislation from Congress, or the agency’s view on the role of FTC prosecution and settlements in light of the two agencies’ often overlapping jurisdiction.

B. FDA Implementation

The FDA currently requires some seventy REMS for approved drug products, with approximately half of those REMS in the form of ETASU.¹⁰⁰ Drugs such as Androgel (testosterone), Mifeprex (mifepristone), Thalomid (thalidomide), and Xeljanz (tofacitinib) all carry REMS ranging from Medication Guides for patients to rigorous ETASU involving elements such as prescriber and/or pharmacist training and registration, notification to relevant professionals, reporting and monitoring, and distribution limitations. If an approved drug has entered the market as a generic drug, it is obligated to follow the listed drug REMS, subject to the considerations described in the statute.

Celgene’s Thalomid provides a prime example of an extensive ETASU, stemming from the serious risks of embryo-fetal exposure to the drug product. The FDA has required that all prescribing healthcare providers are specifically certified, that all patients are informed of the risks of use and exposure to unborn children, that all patients are enrolled in a special program, and that all patient use is actively monitored (and particularly for instances of pregnancy).¹⁰¹ The FDA has also established a restricted distribution program for the Thalomid, which was developed by Celgene and is the subject of

⁹⁹ 21 U.S.C. § 355-1(f)(8) (2013).

¹⁰⁰ See F.D.A., APPROVED REMS, *supra* note 12. There are over seventy individual REMS and six shared system REMS as of June 15, 2015. *Id.*

¹⁰¹ Thalomid REMS, *supra* note 18.

patent protection.¹⁰² This will be discussed in the next section.

The overwhelming majority of REMS address individual drugs, although the FDA has implemented several shared REMS systems that involve ETASU for particular classifications of drugs.¹⁰³ For example, the July 2012 REMS for all opioid drug products have detailed ETASU provisions to assure that prescribers are aware of product-specific prescription requirements.¹⁰⁴ The ETASU requires training to prescribing healthcare providers, which must be offered by accredited providers and must achieve specific performance goals.¹⁰⁵ Independent audits of the educational materials must also be conducted by the training providers.¹⁰⁶ The drug approval holder is responsible for several notification measures: they must maintain a website about the REMS information, they must electronically or directly deliver letters to Drug Enforcement Agency-registered prescribers who may prescribe Schedule I and II drugs notifying of the existence of the REMS, they must electronically or directly deliver letters to named professional organizations and state licensing entities with a request to disseminate to all members, and they must implement a single toll-free telephone number to serve as a centralized call center for all inquiries about the REMS.¹⁰⁷

There is no consensus on how to measure whether REMS are effective to assure that benefits of an approved drug continues to outweigh the risks. A February 2013 Office of the Inspector General report based on REMS approved between 2008 and 2011 questioned whether FDA has sufficient data to determine whether REMS actually improve drug safety.¹⁰⁸ Feedback from physicians and

¹⁰² *See id.*

¹⁰³ The six shared REMS systems are for the following categories of drug products: Buprenorphine Transmucosal Products for Opioid Dependence (BTOD), Extended-Release and Long-Acting (ER/LA) Opioid Analgesics, Isotretinoin, Mycophenolate, Rosiglitazone, and Transmucosal Immediate-Release Fentanyl (TIRF) Products. F.D.A., APPROVED REMS, *supra* note 12.

¹⁰⁴ FOOD AND DRUG ADMIN., EXTENDED RELEASE (ER) AND LONG-ACTING OPIOID ANALGESIC RISK EVALUATION AND MITIGATION STRATEGY (REMS), REF. ID 3612128 (Initial REMS Approval 7/2012; Most Recent Modification 8/2014).

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

¹⁰⁷ *Id.* at 4.

¹⁰⁸ HEALTH AND HUMAN SVC., OFFICE OF INSPECTOR GENERAL, FDA LACKS COMPREHENSIVE

industry suggests that there is a need for standardization of REMS requirements rather than individualized strategies. The FDA continues to refine its approach to REMS, and many REMS have been subject to revisions following approval.

IV. RESTRICTING ACCESS THROUGH REMS

A. Refusing Access to Competitors for Bioequivalence Testing

Brand pharmaceutical companies have recently begun refusing access to their drugs for bioequivalence testing on the basis of REMS distribution restrictions contained in ETASU, resulting in a blockage of generic drug products from entering onto the market. Beginning in 2009, generic sponsors began to complain about this behavior from Celgene, who refused to sell samples of both Thalomid and Revlimid, which are both subject to extensive ETASU.¹⁰⁹ Lannett filed a lawsuit against Celgene for their refusal to provide samples; the lawsuit was ultimately settled on confidential terms.¹¹⁰ However, the attorney general in the state of Connecticut and the FTC initiated investigations into the matter, which were reportedly ongoing in 2013.¹¹¹ In a related matter, Actelion Pharmaceuticals filed for declaratory relief for a determination that they were under no affirmative duty to provide generic applicants Apotex and Roxanne with samples of its Tracleer (bosentan) drug product for purposes of bioequivalence testing.¹¹² Traceleer, like Thalomid and Revlimid, is

DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY (Feb. 2013), available at <https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf>.

¹⁰⁹ See Thalomid and Revlimid REMS, *supra* note 18 and 19.

¹¹⁰ Erin Coe, *Lannett Cuts Deal with Celgene in Thalomid Antitrust Case*, LAW 360 (Dec. 7, 2011), <http://www.law360.com/articles/291483/lannett-cuts-deal-with-celgene-in-thalomid-antitrust-case>.

¹¹¹ Katie Thomas, *Drug Makers Use Safety Rule to Block Generics*, N.Y. TIMES (Apr. 13, 2013) available at <http://www.nytimes.com/2013/04/16/business/drug-makers-use-safety-rule-to-block-generics.html>.

¹¹² Kurt R. Karst, *Actelion Seeks Judgment on the Pleadings in Lawsuit over Restricted Distribution and Biostudy Product Availability*, FDA LAW BLOG (Jan. 23, 2013) http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/01/actelion-seeks-judgment-on-the-pleadings-in-lawsuit-over-restricted-distribution-and-biostudy-product.html.

also subject to ETASU.¹¹³ Actelion claimed a “right to choose with whom it does business,” citing Supreme Court precedent.¹¹⁴ As additional support, Actelion argued that Congress has twice rejected legislation that would include within the REMS provisions the requirement that a brand-name manufacturer bound by an ETASU REMS must sell its drug products to competitors.¹¹⁵ The case was settled in February 2014 on undisclosed terms among the parties.¹¹⁶

The most recent case dealing with a refusal to distribute is *Mylan Pharmaceuticals v. Celgene Corporation*, filed in the U.S. District Court of New Jersey on April 3, 2014.¹¹⁷ Although Mylan recognizes that both drugs at issue (Thalomid and Revlimid) are subject to rigorous distribution restrictions as a result of REMS, they assert that Celgene has used these restrictions as a “pretext to prevent Mylan from acquiring the necessary samples to conduct bioequivalence testing.”¹¹⁸ Mylan alleges that Celgene has engaged in a prolonged scheme, involving themselves as well as wholesale distributors, to “continuously prevent and/or stall all of Mylan’s efforts from

¹¹³ Actelion Clinical Research, Inc., New Supplement for NDA 21-290, Tracleer (bosentan), Risk Evaluation Mitigation Strategy (REMS) Modification (Nov. 15, 2012), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM337919.pdf>.

¹¹⁴ Karst, *supra* note 112. Actelion cites *Verizon Communications, Inc. v. Law Offices a/Curtis V. Trinko, LLP*, 540 U.S. 398, 415-416 (2004). Actelion argues that neither of the two exceptions to the general rule that a unilateral refusal to deal does not implicate antitrust liability apply to them. *Id.* First, they argue that they have no prior course of dealing with Apotex and Roxanne; and second, they argue that the refusal does not relate to an “essential facility.” *Id.*

¹¹⁵ *Id.* The first rejected attempt to include such language was in the 2007 amendments containing the REMS authority. The last rejected attempt was the Senate version of the 2012 FDA Safety and Innovation Act. *Id.*; see also Derrick Gingery, *REMS and Generics: GPhA Needs Legislation, Continues Education*, THE PINK SHEET, 5 (Aug. 4, 2014). Policy folks acknowledge that the issue needs to be addressed at the legislative level, in that there is no regulatory solution available to the FDA to address the issue. *Id.*

¹¹⁶ Sarpatwari et al., *supra* note 15.

¹¹⁷ Mylan Original Complaint *supra* note 16 at 3-4. Coverage of the case can be found at Kurt R. Karst, *Another REMS Lawsuit: Mylan Sues Celgene over Thalomid and Revlimid to Obtain Drug Product*, FDA LAW BLOG (Apr. 4, 2014), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/04/another-rems-antitrust-lawsuit-mylan-sues-celgene-over-thalomid-and-revlimid-to-obtain-drug-product.html.

¹¹⁸ Original Complaint at 3-4, *Mylan Pharms. Inc. v. Celgene Corp.*, No. 14-2094 (D.N.J. Apr. 3, 2014).

obtaining any of the drug products.”¹¹⁹ Mylan seeks declaratory relief, treble damages, costs of the lawsuit, attorney’s fees, and injunctive relief.¹²⁰ Emphasizing the detrimental effects of Celgene’s behavior on health care costs and patients directly, the complaint states:

[S]uch conduct harms consumers by denying them the substantial benefits of lower-priced generic competition and forces consumers and federal, state, and private payers to overspend on prescriptions for these products. Indeed, but for Celgene’s unlawful conduct, consumers and federal, state, and private payors would have enjoyed lower-priced alternatives to Thalomid and Revlimid substantially earlier. Worse yet, left unchecked, there is no end in sight to Celgene’s anticompetitive scheme to block generic competition to these products, to the detriment of Mylan and consumers of these products alike.¹²¹

Mylan references both the Hatch-Waxman Act mandate to generic drug manufacturers to demonstrate bioequivalence to the RLD¹²² and the language of FDAAA that REMS programs were not to be utilized by brand drug manufacturers as a tool to block market entry of generics¹²³ as support for their position. They urge that the practice of refusing access to samples for research and development of generic drugs based on REMS provisions undermines the “careful balance” created by the generic drug approval process¹²⁴ and violates antitrust laws. The complaint states that the FDA has indicated that it will exercise enforcement discretion with regard to the interplay between the Hatch-Waxman Act’s requirement for bioequivalence studies and the recently added REMS distribution limitations.¹²⁵ The FDA has stated that it “would not consider the provision of samples of an RLD [reference listed drug] to a generic manufacturer a REMS violation” because it would frustrate Congressional intent; thus they

¹¹⁹ *Id.* at 4.

¹²⁰ *Id.* at 5.

¹²¹ *Id.* The complaint measures the cost of the drugs to critically ill patients at \$5,000-9,000 per month for Thalomid and \$13,000 per month for Revlimid. *Id.* They claim that the two drugs account for between 71-93% of the company’s yearly revenue. *Id.*

¹²² 21 U.S.C. § 355(j)(2)(iv) (2012).

¹²³ 21 U.S.C. § 355-1(f)(8).

¹²⁴ Original Complaint at 12, *Mylan Pharms. Inc. v. Celgene Corp.*, No. 14–2094 (D.N.J. Apr. 3, 2014).

¹²⁵ *Id.* at 11.

would not impose penalties.¹²⁶ As discussed in Part III A, the FDA has espoused this position in recent draft guidance to industry.¹²⁷

Two months after Mylan filed the lawsuit, the FTC filed an amicus brief in support on both aspects: that Celgene's behavior thwarts the intent of Congress in passing the Hatch-Waxman Act and potentially violates key provisions of the federal antitrust law.¹²⁸ On the antitrust front, the FTC brief emphasizes that a refusal to sell to rivals may violate Section 2 of the Sherman Act, while vertical agreements (such as those between Celgene and its distributors) may violate Section 1.¹²⁹ As support for violations of Section 2, the FTC points to several Supreme Court cases finding that exclusionary conduct is identifiable by its tendency to "impair the opportunities of rivals" and "either does not further competition on the merits or does so in an unnecessarily restrictive way."¹³⁰ The FTC urges that the fact that Celgene is willing to provide non-competitors with access to both Thalomid and Revlimid despite distribution restrictions, while refusing access to its potential competitors at full compensation, supports the presence of exclusionary conduct on the part of Celgene.¹³¹

As support for violations of Section 1, the FTC notes that vertical agreements may sometimes have the effect of "reducing effect among horizontal competitors" and may therefore be violations of the Sherman Act.¹³² The FTC provides that such vertical agreements are then subject to the rule-of-reason analysis.¹³³ Citing *FTC v. Actavis*, the FTC advances the position that Celgene's assertions of valid patent protection "do not by themselves demonstrate a lack of antitrust injury" and that instead the rule-of-reason analysis must dictate the

¹²⁶ *Id.*

¹²⁷ *FDA Draft Guidance: How to Obtain a Letter*, *supra* note 89.

¹²⁸ Brief for Fed. Trade Comm'n as Amicus Curiae, *Mylan Pharm. Inc. v. Celgene Corp.*, No. 14-2094 (D.N.J. June 17, 2014).

¹²⁹ *Id.* at 8.

¹³⁰ *Id.* at 10 (citing *Aspen Skiing Co. v. Aspen Highlands Skiing Corp.*, 472 U.S. 585, 605 (1985) (quoting Phillip Areeda & Donald F. Turner, *ANTITRUST LAW* 79 (1978)).

¹³¹ *Id.* at 14.

¹³² *Id.* at 17.

¹³³ *Id.*

outcome.¹³⁴

The December 22, 2014 decision in the U.S. District Court of New Jersey denied Celgene's motion to dismiss claims regarding Section 2 of the Sherman Act and dismissed Mylan's allegations under Section 1.¹³⁵ Judge Salas found that Mylan sufficiently pled evidence of monopolization and "the willful acquisition or maintenance of that power as distinguished from growth or development as a consequence of a superior product, business acumen, or historic accident" to survive dismissal of the Section 2 claims.¹³⁶ However, as to Section 1, Judge Salas found that the complaint failed to assert non-conclusory allegations regarding an unlawful agreement between Celgene and distributors giving rise to liability.¹³⁷ The Third Circuit declined Celgene's appeal for immediate review in March 2015.¹³⁸

In addition to outright refusals to supply samples for means of bioequivalence studies, many generic companies are also finding that brand manufacturers are unwilling to work with them on the development of single, shared REMS systems. Following unsuccessful attempts at negotiating with brand name drug manufacturers, several generic companies have petitioned the FDA for guidance on how to coordinate a single, shared REMS program when the brand-listed drug refuses such collaboration.¹³⁹ Under the terms of the statute, FDA may waive certain elements of a shared REMS system, though there is no direction provided to generic applicant on their role in the process and upon what factors the FDA will consider such a waiver.¹⁴⁰ The statute provides no direction on how to coordinate a single, shared REMS approach, and whether and to what extent the FDA has any authority to require such

¹³⁴ *Id.* at 17, 20.

¹³⁵ Mylan Order on Motion to Dismiss, *supra* note 26.

¹³⁶ *Id.* at 9, *citing* Verizon Comm., Inc. v. Law Offices of Curtis V. Trinko, L.L.P., 540 U.S. 398, 407 (2004) (*quoting* United States v. Grinnel Corp., 384 U.S. 563, 570-71 (1966)).

¹³⁷ *Id.* at 24.

¹³⁸ Gurrieri, *supra* note 27.

¹³⁹ Ed Silverman, *Share and Share Alike? Not if it's a REMS*, DRUGS.COM (Dec. 2013), http://www.drugs.com/clinical_trials/share-share-alike-not-if-s-rems-16362.html?utm_source=ddc&utm_medium=rss&utm_campaign=rss.

¹⁴⁰ *See* 21 U.S.C. § 355-1(i)(1)(B).

coordination.

Two citizens' petitions have been filed by generic pharmaceutical manufacturers in an effort to achieve more direction on the application of the terms of the statute and the FDA's role in collaborative efforts between companies. Dr. Reddy filed their petitions in June 2009, which were granted in part, denied in part in August 2013.¹⁴¹ Dr. Reddy had asked the FDA to establish procedures in order to facilitate the market entry of generic drugs onto the market that are subject to a REMS and to appropriately enforce the statute to prevent listed drug manufacturers from blocking generic competition through use of REMS.¹⁴² Prometheus Laboratories filed a similar petition in May 2013, which was denied by the FDA in October 2013.¹⁴³ The FDA has acknowledged that it is currently evaluating whether guidance or rulemaking on the subject would be useful although it has declined to act in response to either petition, instead relying on a case-by-case approach.¹⁴⁴ In response to Prometheus's concern about the implications for antitrust law, the FDA stated: "[t]o the extent that Prometheus believes there may be antitrust issues associated with establishing single, shared systems. . .it [should] consult with the FTC."¹⁴⁵ Again, as discussed earlier, the FDA's position may be based on any number of factors, including agency priorities, fiscal considerations, pending legislation, or view on the role of the FTC in pursuing prosecution or settlements in this area.

B. Patenting Patient Treatment and Delivery Methods

Another REMS-focused tactic is the RLD manufacturer's assertion of patent rights over elements contained within an FDA-approved ETASU to block generic use of the REMS. Under the federal patent statute, patents may be issued to "[w]hoever invents or

¹⁴¹ Silverman, *supra* note 139.

¹⁴² *Id.*

¹⁴³ *Id.*

¹⁴⁴ *Id.*

¹⁴⁵ Kurt R. Karst, *FDA Largely Denies Citizen Petition on Single Shared REMS But Outlines Agency Standards and Processes*, FDA LAW BLOG (Oct. 21, 2013), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/10/fda-largely-denies-citizen-petition-on-single-shared-rems-system-but-outlines-agency-standards-and-p.html.

discovers any new and useful process, machine, manufacture, or composition of matter.”¹⁴⁶ Substantive patent law requires that an invention be useful,¹⁴⁷ novel,¹⁴⁸ nonobvious,¹⁴⁹ and have an adequate written description.¹⁵⁰ Each of these requirements is specifically established in the statute, patent examiner manual, and case law. Because of their nature, claims to ETASU will be set forth as process claims. Process claims, more commonly referred to as method claims, are defined by the United States Patent and Trademark Office (USPTO) as “an act, or a series of acts or steps.”¹⁵¹ Claims specifically enumerate the features of the invention in precise, technical language and terms of art.

As an example of this assertion of patent rights for ETASU, Celgene has patented its distribution program in U.S. Patent No. 7, 141, 018 B2, entitled *Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated*.¹⁵² The patent abstract describes the invention as “[m]ethods for delivering a drug to a patient in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated.”¹⁵³ The patent specifically claims methods over prescription drug filling by a pharmacy employing a computer readable storage medium and prescription approval codes.¹⁵⁴ The nine enumerated claims are as follows:

1. A method for treating a patient having a disease or condition which is responsive to thalidomide while restricting access to thalidomide for patients for whom thalidomide may be contraindicated, the method comprising permitting prescriptions for thalidomide to be filled by a pharmacy only after the pharmacy has become aware of the generation

¹⁴⁶ 35 U.S.C. § 101 (2014).

¹⁴⁷ *Id.*

¹⁴⁸ 35 U.S.C. § 102 (2014).

¹⁴⁹ 35 U.S.C. § 103 (2014).

¹⁵⁰ 35 U.S.C. § 112 (2014).

¹⁵¹ U.S. Patent and Trademark Office, Manual of Patent Examining Procedure # 2106 (*quoting* *Gottschalk v. Benson*, 409 U.S. 63, 70 (1972)).

¹⁵² *Methods for Delivering a Drug to a Patient While Restricting Access to the Drug by Patients for Whom the Drug May be Contraindicated*, U.S. Patent No. 7,141,018 B2 (filed Nov. 28, 2006).

¹⁵³ *See Id.* at Abstract.

¹⁵⁴ *Id.*

of a prescription approval code for thalidomide for the patient from a computer readable storage medium, the generation of said prescription approval code comprising the following steps: a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for thalidomide; b. defining a set of information to be obtained from the patient, said set of information comprising the result of a determination of the ability of the patient to become pregnant and optionally comprising a determination that the patient is either (1) not currently pregnant or (2) currently pregnant; c. in response to said information set, assigning the patient to at least one of said risk groups and entering the patient, the information and the patient's risk group assignment into the medium; d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and e. upon a determination that the risk is acceptable, generating the prescription approval code before the prescription is filled.¹⁵⁵

2. A method according to claim 1 further comprising registering in the medium the physician who prescribed said thalidomide.

3. A method according to claim 1 further comprising registering the pharmacy in the medium.

4. The method of claim 1 further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

5. The method of claim 4 wherein the counseling comprises full disclosure of the risks.

6. The method of claim 5 wherein the prescription is filled only following said full disclosure.

7. The method of claim 6 wherein the fact of said full disclosure is registered in the computer readable storage medium prior to generation of the prescription approval code.

8. The method of claim 7 wherein the risk group assignment and the fact of said full disclosure is transmitted to the computer readable storage medium by facsimile and interpreted by optical character recognition software.

9. The method of claim 1 further comprising: f. defining for each risk group a second set of information to be collected from the patient at periodic intervals; g. obtaining the second set of information from the patient; and h. entering the second set of information in the medium.¹⁵⁶

¹⁵⁵ *Id.* at Claims.

¹⁵⁶ *Id.*

The scope of patent claims that are integrated into existing REMS in the form of ETASU has drawn criticism from a variety of legal and policy sources.¹⁵⁷ The core argument is that the proprietary nature of patent law is not amenable to methods for the delivery of patient care, where the inability to utilize a listed drug REMS may reduce the safety of a different procedure employed by a generic competitor. The inability to utilize the REMS of the listed drug also technically violates the requirement that a generic drug carry the same label as the listed drug. Similar to arguments against refusals to distribute drug samples for purposes of bioequivalence testing, opponents say that such patents conflict with the Congressional aim of a shared REMS system as set forth in the legislation.¹⁵⁸

Recent Supreme Court precedent in the realm of patentable subject matter also raises questions for patents covering REMS elements. The Supreme Court, through case law, has excluded from patentable subject matter laws of nature, natural phenomena, and abstract ideas. Anything falling within these three categories is deemed “part of the storehouse of knowledge of all men. . . free to all men and reserved exclusively to none.”¹⁵⁹

Over a hundred years of Supreme Court precedent explores the bounds of patentable subject matter and several cases over the past five years are particularly informative here. In 2014, in *Alice Corporation v. CLS Bank International*, a unanimous Supreme Court held that method claims for a computer-implemented process for mitigation of settlement risk are not patent eligible subject matter.¹⁶⁰

¹⁵⁷ See Sue Sutter, *Should Patents on REMS Distribution Restrictions Be Banned?*, THE PINK SHEET DAILY, Apr. 17, 2014; Denise Daley, *Patenting ETASU Programs to Delay Competition from Generic Drugs*, KULKARNI LAW FIRM BLOG (Jan. 8, 2013), <https://www.conformlaw.com/blog/patenting-etasu-programs-to-delay-competition-from-generic-drugs/>; LAURA S. SHORES, PEPPER HAMILTON LLP, *Pharmaceutical Patent Life Extension Strategies: Are REMS Programs Next?* (Mar. 28, 2012), http://www.pepperlaw.com/uploads/files/shores_antitrustchronicle_0312.pdf; Stephen B. Maebius, et al, *Patenting Risk Evaluation and Mitigation Strategies for Pharmaceuticals: A New Life Cycle Management Target for Patents?*, 7 BNA PHARMACEUTICAL LAW & INDUSTRY REPORT 1-3 (2009); Maxmillian A. Grant, et al., *Not Yet: Patented Risk Evaluation and Mitigation Strategies May Delay (or Tax) Competitors*, INTELL. PROP. TODAY 10-12 (June 2009).

¹⁵⁸ Sutter, *supra* note 157.

¹⁵⁹ Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948).

¹⁶⁰ *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2349, 2352-53 (2014). The representative method claim recites the following steps: (1) “creating” shadow records for each

Justice Thomas framed the relevant question for the court as “whether the claims here do more than simply instruct the practitioner to implement the abstract idea of intermediated settlement on a generic computer.”¹⁶¹ He responded, “[t]hey do not.”¹⁶² An excerpt from the Slip Opinion syllabus succinctly describes the reasoning of the court:

Here, the representative method claim does no more than simply instruct the practitioner to implement the abstract idea of intermediated settlement on a generic computer. Taking the claim elements separately, the function performed by the computer at each step—creating and maintaining “shadow” accounts, obtaining data, adjusting account balances, and issuing automated instructions—is “[p]urely ‘conventional.’” *Mayo*, 566 U. S., at 1299. Considered “as an ordered combination,” these computer components “ad[d] nothing . . . that is not already present when the steps are considered separately.” *Id.*, at 1291. Viewed as a whole, these method claims simply recite the concept of intermediated settlement as performed by a generic computer. They do not, for example, purport to improve the functioning of the computer itself or effect an improvement in any other technology or technical field. An instruction to apply the abstract idea of intermediated settlement using some unspecified, generic computer is not “enough” to transform the abstract idea into a patent-eligible invention.¹⁶³

Prior to *Alice Corp. v. CLS Bank*, three other recent high profile Supreme Court decisions applied this patentable subject matter precedent to several modern day technologies. Two of them dealt with method claims,¹⁶⁴ while the third dealt with composition of matter claims.¹⁶⁵ The two method claim cases are directly relevant to

counterparty to a transaction; (2) “obtaining” start-of-day balances based on the parties’ real-world accounts at exchange institutions; (3) “adjusting” the shadow records as transactions are entered, allowing only those transactions for which the parties have sufficient resources; and (4) issuing irrevocable end-of-day instructions to the exchange institutions to carry out the permitted transactions. *Id.* at 2353.

¹⁶¹ *Id.* at 2359.

¹⁶² *Id.*

¹⁶³ *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, No. 13-298, slip op., at 3 (U. S. June 19, 2014).

¹⁶⁴ See *Bilski v. Kappos*, 130 S. Ct. 3218 (2010); *Mayo Collaborative v. Prometheus Lab.*, 132 S. Ct. 1289 (2012).

¹⁶⁵ See *Ass’n for Molecular Pathology v. Myriad Genetics*, 133 S. Ct. 2107 (2013). This case challenged the validity of composition of matter claims issued by the USPTO for isolated sequences of DNA associated with predisposition to breast and ovarian cancers. The Supreme Court determined that an isolated segment of naturally-occurring DNA is a

the REMS patents and were cited heavily in *Alice Corp.* The first of these cases, *Bilskiv. Kappos*,¹⁶⁶ involved patent claims related to the interaction of buyers and sellers of commodities in the energy market and hedging against the risk of price fluctuations. The two method claims at issue in the case together “describe a series of steps instructing how to hedge risk” through transactions between commodity providers, consumers, and market participants and “put[] the concept. . .into a simple mathematical formula.”¹⁶⁶ The USPTO rejected the claims because they involved mental steps that do not transform physical matter and were directed to an abstract idea.¹⁶⁷ The Supreme Court agreed, finding the claims drawn to an abstract idea and thus not patentable subject matter.¹⁶⁸

The second previous case, *Mayo Collaborative Services et al. v. Prometheus Laboratories*, involved method claims to aid doctors in prescribing thiopurine drugs to patients with autoimmune diseases.¹⁶⁹ The claims before the court involved a three-step process, essentially measuring levels of a medication, reading the levels, and determining whether an administered dose is likely to produce toxic side effects.¹⁷⁰ The Court concluded that the claimed processes did not transform a

product of nature and is not patentable. *Id.*

¹⁶⁶ *Bilski*, 130 S. Ct. at 3223-24. For example, claim 1 laid out the following steps: “(a) initiating a series of transactions between said commodity provider and consumers of said commodity wherein said consumers purchase said commodity at a fixed rate based upon historical averages, said fixed rate corresponding to a risk position of said consumers; (b) identifying market participants for said commodity having a counter-risk position to said consumers; and (c) initiating a series of transactions between said commodity provider and said market participants at a second fixed rate such that said series of market participant transactions balances the risk position of said series of consumer transactions.” *Id.*

¹⁶⁷ *Id.* at 3224.

¹⁶⁸ *Id.* at 3231.

¹⁶⁹ *Mayo Collaborative*, 132 S. Ct. at 1289.

¹⁷⁰ *See id.* at 1295. For example, claim 1 of the patent describes one of the claimed processes as follows: “A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per 8×10⁸ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per 8×10⁸ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject [. . .].” *Id.*

non-patentable natural law into a patent eligible application of those laws.¹⁷¹ The Court stated that, “while it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action.”¹⁷² According to the Court, a patent claim must “add enough to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that apply natural laws.”¹⁷³ The method claims failed because the instructions were a phenomenon of nature, which “add nothing specific to the laws of nature other than what is well-understood, routine, conventional activity, previously engaged in by those in the field.”¹⁷⁴

These Supreme Court cases dealing with the interpretation of the scope of method claims are instructive to assessment of the ETASU patent claims for several related reasons. First, all of these cases were decided subsequent to the granting of Celgene’s Thalomid ETASU patent in 2008. At that time, the USPTO and the Federal Circuit were construing method claims in a manner later invalidated or narrowed by the Supreme Court in *Alice Corp, Bilski*, and *Mayo*. Second, Celgene’s ETASU patent claims are drawn to a computer medium, similar to *Alice Corp*. There, the Supreme Court made clear that the implementation of an abstract idea on a generic computer did not involve patentable subject matter. Third, the claims simply describe mental steps and place them into a formulaic construct, similar to *Bilski*. Fourth, the claims describe natural relationships that exist among patients and third parties as part of the prescription drug process, similar to *Mayo*.

The USPTO issued interim guidance in December 2014 representing the agency’s views on patentable subject matter assessments following the Supreme Court decisions in these cases.¹⁷⁵ Step One asks whether the invention claims a process, machine,

¹⁷¹ *Id.* at 1305.

¹⁷² *Id.* at 1297.

¹⁷³ *Id.*

¹⁷⁴ *Id.* at 1299.

¹⁷⁵ U.S. PATENT & TRADEMARK OFFICE, 2014 INTERIM GUIDANCE ON PATENT SUBJECT MATTER ELIGIBILITY, 79 Fed. Reg. 74618 (Dec. 16, 2014)(to be codified at 37 C.F.R. pt. 1).

manufacture, or composition of matter.¹⁷⁶ If yes, then the assessment is to proceed to Step 2A, which asks whether the invention is drawn to a law of nature, natural phenomenon, or abstract idea.¹⁷⁷ If yes, the assessment is to proceed to Step 2B, which asks whether the invention claims additional elements that amount to “significantly more” than the judicial exception.¹⁷⁸ If they do not add significantly more, than the claim is not patentable subject matter; if they do add significantly more, than the claim is patentable subject matter.¹⁷⁹ These interim guidelines are effective, though the USPTO has requested public comments until March 16, 2015.¹⁸⁰

Given the USPTO guidance, an important question for new patent claims covering distribution elements contained in REMS is whether they add significantly more to an abstract idea or phenomenon of nature. Patent examiners will apply this test to incoming patent applications, though the courts are not legally bound to apply the guidance and will interpret and apply the Supreme Court precedent as they see fit to existing patents. Coverage of lower court decisions applying the Supreme Court’s patentable subject matter framework suggests that it is an increasingly critical threshold defense and that lower courts are routinely using Alice Corp. to invalidate claims to computer-implemented inventions.¹⁸¹

V. SHORT AND LONG-TERM REMEDIES

The problems identified in the previous sections are fairly recent developments, with the FDA and FTC just beginning to identify strategies to address the short and long-term implications. This

¹⁷⁶ *Id.* at 74621.

¹⁷⁷ *Id.*

¹⁷⁸ *Id.*

¹⁷⁹ *Id.*

¹⁸⁰ *Id.* at 74619.

¹⁸¹ See LATHAM & WATKINS, *Client Alert Commentary, No. 1744*, (Sept. 19, 2014) <http://www.lw.com/thoughtLeadership/lw-alice-corp-cls-bank-section-101>; Frank Amini, *Alice in Wonderland: The Ongoing Impact of Alice Corp. v. CLS Bank Int'l on Computer-Implemented Inventions*, WINTECH (Oct. 6, 2014), <http://www.wintechblog.com/2014/10/alice-in-wonderland-the-ongoing-impact-of-alice-corp-v-cls-bank-intl-on-computer-implemented-inventions/>.

section offers preliminary thoughts on approaches to these issues given the applicable law, Congressional will, and agency inertia. Subsequent research, analysis, and publications will further explore and elucidate these initial thoughts.

A. Drug Access

Behaviors of the pharmaceutical industry adapt to developments in the law and regulations. The area of REMS is no different and will continue to play out in the marketplace. There are several approaches to address perceived problems with the use of REMS restrictions, and ETASU in particular, to block generic access to listed drug samples. Although there is pending antitrust litigation as discussed earlier, its resolution is uncertain. Similar to previous actions against Celgene for such behavior, the case may settle. If it progresses, the outcome and appeal process will take years.

The most direct approach to dealing with the issue outside of antitrust litigation is an explicit amendment to the FDCA, although its enactment could take years given the current climate in Congress. Multiple sources have pointed out previous attempts to add affirmative requirements into the FDCA to force listed drug manufacturers to provide access to drug samples for purposes of bioequivalence testing; such provisions were contained in both the original bills that later became 2007 FDAAA, as well as the 2012 Food and Drug Safety and Innovation Act.¹⁸² The legislative history of both bills sheds little light on why these provisions were ultimately removed from the enacted legislation. However, the recent H.R. 5657 would resolve this issue by adding explicit language mandating that RLD sponsors provide access at commercially reasonable prices or be subject to enforcement and private action.

Another approach is the promulgation of regulation by the FDA, or, in the alternative, guidance in the form of a guidance document or series of related guidance documents for industry. This is also time-consuming, and it does not appear to be favored by the FDA at this point in time. The FDA has to date expressed a reluctance to proceed other than on a case-by-case basis with regard to REMS collaborations, though it has sought input from industry on feasible

¹⁸² Pub. L. 112-144 (2012).

approaches going forward. If inspired to act, the FDA could rely on its general rulemaking authority under the Hatch-Waxman Act to promulgate regulations in this area. Based on the strong legislative history, portraying a universal concern about anticompetitive behavior and the goal of a vibrant generic drug market, such regulation seems to be easily legally defensible. However, the FDA could also proceed in the short term with a guidance document that identifies mechanisms to support and reward collaboration. While not legally binding as regulations would be, guidance documents have incredible force in the FDA realm and would provide a useful step here.

A third approach is the creation of incentives to deal, either through statute or FDA policy. These incentives may be in the form of exclusivities, as with new chemical entities, pediatric indications, and orphan drugs. Here, RLD sponsors could be awarded a certain period of exclusivity on the market for agreeing to widely share access to product samples for bioequivalence testing by generic applicants. Alternatively, the FDA may develop a priority review voucher program similar to that established for tropical diseases.¹⁸³ RLD sponsors could thus receive a voucher for a priority (faster) review of an application in return for licensing and access. This approach, however, presupposes either that the statute or FDA regulation or policy does not require the RLD sponsor to provide access; or that such an action preventing generic access is not a violation of antitrust law.

B. Patent Scope

The landscape of patent law as it applies to pharmaceutical compounds and methods is extremely challenging. As noted earlier, the statute enables the USPTO to grant patents for inventions that are useful, novel, non-obvious, and adequately described in the written description, which consists, in part, of the enumerated claims.¹⁸⁴ Where an applicant satisfies all the substantive requirements for a patent, yet the effect of the patent is to remove a method from public

¹⁸³ FOOD AND DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: TROPICAL DISEASE PRIORITY REVIEW VOUCHERS (Oct. 2008) *available at* <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0530-gdl.pdf>.

¹⁸⁴ 35 U.S.C. §§ 101, 102, 103, 112 (2012).

use subject to a license, questions arise as to whether the monopolistic effect is in the public interest. Nowhere has this question been more prevalent than in the medical and healthcare realm.

Assuming that a drug sponsor or manufacturer holds a valid patent on a method for specific utilization of a drug product, the holder of the patent then has an effective 20-year monopoly over the use of that method by anyone else.¹⁸⁵ In the Hatch-Waxman Act, Congress amended both the FDCA and the patent law to create a mechanism to allow generic drug sponsors to challenge granted patents through the paragraph IV procedure. However, even this mechanism focuses only on the substantive requirements of patent law in determining whether an existing patent is valid. Broader public policy concerns, such as access to drug delivery methods and processes described in ETASU, are not part of the substantive patent law.

The recent case law in the realm of patentable subject matter provides one approach to addressing the issue of REMS patent claims. However, as previously noted, interpretation by the lower courts is only beginning, and the USPTO guidance on the subject lacks rigorous application. Also, by law, in order for a generic applicant to challenge an already-granted patent, they can assert invalidity only as a defense to an infringement action brought by the patent holder,¹⁸⁶ or have submitted a challenge to a granted patent within nine months from the date of issuance by the USPTO through a process called *post grant review*.¹⁸⁷ This significantly limits the timing and availability of judicial review, making this less than an ideal vehicle to address the current REMS claim scope. Another mechanism, called *inter partes review*, provides the ability to challenge an issued patent on grounds of lack of novelty or obviousness.

In order to directly address the ill-effects of the patenting of REMS, and ETASU in particular, the scope of the statute and FDA regulations need to be tested. Restrictions imposed by RLD sponsors through patent rights are antithetical to the spirit of Hatch-Waxman and the REMS provisions, which rely on concepts of identical

¹⁸⁵ 35 U.S.C. § 154 (2014). This is measured from the date of the filing of the application. *Id.*

¹⁸⁶ 35 U.S.C. § 282(b)(2) (2014).

¹⁸⁷ 35 U.S.C. § 311.

labeling and product information absent exceptional circumstances. Patent rights to distribution aspects enshrined in REMS remove these aspects from the public domain, and force generic applicants to either adopt a less safe and effective mechanism for their REMS, or avoid the generic market altogether. This places patient safety at risk, severely limits patient choice, and raises health care costs. Ideally, the FDA should interpret existing statutory provisions through regulation specifically targeting patenting behaviors. This would undeniably be challenged by industry as a violation of the Administrative Procedures Act, though FDA's wide-reaching authority to promulgate regulations to effectuate the statute would likely prevail.

Congress may also act by amending the patent law in a number of ways. Congress could either explicitly prohibit patents on REMS elements altogether, or amend the patent law to prohibit infringement actions against generic drug sponsors for use of patented REMS. Explicit prohibition of patents for distribution elements contained in REMS would achieve the end result most effectively, but could possibly raise challenges under international patent treaties. If Congress were to proceed through a limitation on infringement actions, they have a model to use. In the past, responding to litigation against a medical doctor, Congress created a safe harbor for medical practitioners to use patented medical procedures. Known as the Physician Immunity Statute,¹⁸⁸ the amendments place limitations on patent infringement suits by the patent holder rather than an outright ban on such patents. The provisions read:

(c)(1)With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b), the provisions of sections 281, 283, 284, and 285 shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.

(2)For the purposes of this subsection:

(A) the term "medical activity" means the performance of a medical or surgical procedure on a body, but shall not include

¹⁸⁸ For a discussion of the historical development of the Physician Immunity Statute, see Jeff S. Rundle, *The Physician's Immunity Statute: A Botched Operation or a Model Procedure?*, 34 J. CORP. L. 944, 944-966 (2009).

(i) the use of a patented machine, manufacture, or composition of matter in violation of such patent,

(ii) the practice of a patented use of a composition of matter in violation of such patent, or

(iii) the practice of a process in violation of a biotechnology patent.

(B) the term “medical practitioner” means any natural person who is licensed by a State to provide the medical activity described in subsection (c)(1) or who is acting under the direction of such person in the performance of the medical activity.

(C) the term “related health care entity” shall mean an entity with which a medical practitioner has a professional affiliation under which the medical practitioner performs the medical activity, including but not limited to a nursing home, hospital, university, medical school, health maintenance organization, group medical practice, or a medical clinic.

(D) the term “professional affiliation” shall mean staff privileges, medical staff membership, employment or contractual relationship, partnership or ownership interest, academic appointment, or other affiliation under which a medical practitioner provides the medical activity on behalf of, or in association with, the health care entity.

(E) the term “body” shall mean a human body, organ or cadaver, or a nonhuman animal used in medical research or instruction directly relating to the treatment of humans.¹⁸⁹

The language applies to “medical practitioners” and “related health care entities” in the performance of “medical activity,” which may apply broadly enough to cover physicians, pharmacists, and other health care individuals in carrying out REMS; however, the language does not cover generic drug sponsors utilizing particular information or methods in REMS. Congress would need to include additional provisions to exactly cover the use of REMS by generics given the scope of their application.

Another approach may be to institute compulsory licensing, requiring the patent holder to allow use of the patented method contained within REMS by the generics. However, this historically has not been an approach favored by the U.S. government and has been instituted on only limited occasions. FDA action, or Congressional amendment, would remedy the issue more directly.

¹⁸⁹ 35 U.S.C. § 287(c) (2012).

VI. CONCLUSION

This article has explored two tactics increasingly exhibited by brand pharmaceutical companies to stifle generic competition: (1) the refusal to supply generic competitors with drug samples for use in bioequivalence testing citing REMS distribution restrictions; and (2) the assertion of patent rights over comprehensive patient treatment and delivery methods contained in FDA-approved REMS. Thus far, these tactics have fostered legal challenges from the FTC, Congressional bills, citizen petitions to the FDA requesting action, and widespread criticism from the generic drug industry and the medical community. After examining the current climate of such activity, this article suggests preliminary thoughts on approaches to addressing these tactics. These include litigation of patent, antitrust, and new drug provisions; Congressional amendments to relevant statutes; and FDA action. Subsequent research, analysis, and publications aim to further explore and elucidate these ideas.