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LIFE WITH A REMS: CHALLENGES AND OPPORTUNITIES

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INTRODUCTION

On September 27, 2007, President George W. Bush signed the Food and Drug Administration Amendments Act of 2007 (FDAAA),¹ ushering in a new regime of postmarket authority for the Food and Drug Administration (FDA). Among other things, FDAAA authorized FDA to require labeling changes, postmarket studies, and Risk Evaluation and Mitigation Strategies (REMS).² Under the last authority, where certain criteria are met, FDA may require a drug manufacturer to propose a REMS—which can range in scope from a simple medication guide to complex and onerous “elements to assure safe use” (ETASU)—as part of a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA), or after a drug has been approved by FDA.³

Prior to FDAAA, certain drug and biologics manufacturers implemented plans designed to mitigate risk (most recently known as “risk management plans” or RiskMAPs).⁴ The critical difference, however, was that these were generally

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1. Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.); *see also* U.S. Food & Drug Admin., Food and Drug Administration Acts (FDAAA) of 2007, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAct/SignificantAmendmentsToTheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm> (last visited May 17, 2010) (detailing the new regulatory Amendments signed into law by President Bush in September 2007).

2. FDAAA § 901(a), 121 Stat. at 922–39 (codified at 21 U.S.C. §§ 355(o)–(p), 355-1 (West Supp. 2009)).

3. *See infra* Part I.A.

4. *See generally* U.S. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY DEVELOPMENT AND USE OF RISK MINIMIZATION ACTION PLANS (2005) (outlining FDA guidance to industry on the development, implementation, and evaluation of RiskMAPs).

voluntary agreements.⁵ In contrast, FDA's new REMS authority gives the agency the power to impose mandatory plans,⁶ and a manufacturer's failure to comply with a requirement of an approved REMS may subject a responsible person to criminal sanctions as well as significant civil monetary penalties.⁷ As a result, both FDA and the companies that the agency regulates are operating in a new environment. FDAAA gave FDA significant new authority and correspondingly expanded its obligations.⁸ Similarly, regulated industry is facing a regulator that is increasingly focused on monitoring products once they are in the marketplace.⁹

Indeed, although authors have begun to chronicle FDA's use of its new REMS authority,¹⁰ very little has been written to date about the practical impact the REMS authority may have on drug manufacturers. This Article therefore addresses some of the challenges and opportunities that manufacturers may face in the post-REMS world,¹¹ including the impact that REMS may have on tort liability¹² and, in

5. Gerald F. Masoudi, *Legal Developments in the Enforcement of Food and Drug Law*, 63 FOOD & DRUG L.J. 585, 586 (2008).

6. 21 U.S.C. § 355-1(a)(1)–(2). If the Secretary determines that a risk evaluation and mitigation strategy is necessary, Section 355-1 provides that an applicant “shall submit to the Secretary as part of such application a proposed risk evaluation and mitigation strategy.” *Id.* § 355-1(a)(1) (emphasis added).

7. Pursuant to Section 505(p) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a responsible person or entity is prohibited from introducing or delivering for introduction into interstate commerce an approved drug that is the subject of any “covered application,” as defined in Section 505-1(b)(2), if a REMS is required with respect to the drug and the person or entity fails to maintain compliance with the requirements of the approved REMS or other requirements under Section 505-1 of the FD&C Act. *Id.* §§ 355(p)(1), 355-1(b)(2); see also *infra* notes 14–16 (discussing the covered applications, which include an NDA, ANDA, and BLA). A violation of Section 505(p) or Section 505-1 is subject to civil monetary penalties of up to \$250,000 per violation, not to exceed \$1 million in a single proceeding. 21 U.S.C. § 333(f)(4)(A)(i). These penalties increase if the violation continues for more than thirty days after FDA notifies the responsible person or entity, doubling for the second thirty-day period and continuing to double for subsequent thirty-day periods, up to \$1 million per period and \$10 million per proceeding. *Id.* § 333(f)(4)(A)(ii). In addition, under Section 502(y) of the FD&C Act, a drug is misbranded if a responsible person or entity fails to comply with a requirement of an approved REMS. *Id.* § 352(y). Misbranding may lead to both criminal and civil penalties, as well as collateral consequences including potential debarment and exclusion from future participation in federal health care programs. See generally *id.* § 333 (providing criminal and civil penalties for violations of § 331, which addresses, *inter alia*, misbranding of drugs); *id.* § 335a (detailing debarment provisions); 42 U.S.C. § 1320a-7(a)–(b) (2006 & West Supp. 2009) (authorizing the exclusion of certain individuals and entities from participation in federal health care programs for certain criminal convictions).

8. See *infra* Part I.

9. See Masoudi, *supra* note 5, at 586 (discussing FDA's authority under FDAAA to change the labeling of a drug once postmarket safety information emerges).

10. See, e.g., *id.* at 586–87 (analyzing the FDAAA provisions relating to REMS); Jeremiah J. Kelly & Michael David, *No Longer “If,” But “When”: The Coming Abbreviated Approval Pathway for Follow-on Biologics*, 64 FOOD & DRUG L.J. 115, 143–44 (2009) (arguing that REMS provisions should be applied to new abbreviated approval pathway for follow-on biologics under the Public Health Service Act).

11. See *infra* Part II.

12. See *infra* Part II.A.

particular, the availability of a preemption defense in the wake of the Supreme Court's recent decision in *Wyeth v. Levine*.¹³

I. BACKGROUND

A. Statutory Authority

Pursuant to its new REMS authority, FDA may require an NDA,¹⁴ ANDA,¹⁵ or BLA¹⁶ applicant to submit a proposed REMS as part of its initial application if, after considering certain factors, the agency “determines that a [REMS] is necessary to ensure that the benefits of the drug outweigh the risks of the drug”¹⁷ FDA also may require the sponsor of an approved NDA, ANDA, or BLA to implement a REMS if the agency “becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.”¹⁸

The only element required for all REMS is a timetable for assessing the REMS' effectiveness; sponsors generally must conduct three such assessments during the seven years following the REMS' approval.¹⁹ In addition, however, FDA may—and as a general matter, does—require additional REMS elements, which range in complexity and in the burden they impose on manufacturers.²⁰ On the least onerous end of the scale, FDA may require the sponsor to create a medication guide

13. 129 S. Ct. 1187 (2009).

14. 21 U.S.C. §§ 355(p)(1), 355-1(b)(2) (West Supp. 2009) (authorizing mandatory REMS for drugs approved under 21 U.S.C. § 355(b) (NDAs)).

15. *Id.* (authorizing mandatory REMS for drugs approved under 21 U.S.C. § 355(j) (ANDAs)).

16. *See id.* (authorizing mandatory REMS for drugs approved under 42 U.S.C. § 262 (BLAs)).

17. *Id.* § 355-1(a)(1). In making its determination, the agency is required to consider:

(A) The estimated size of the population likely to use the drug involved[;] (B) The seriousness of the disease or condition that is to be treated with the drug[;] (C) The expected benefit of the drug with respect to such disease or condition[;] (D) The expected or actual duration of treatment with the drug[;] (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug[; and] (F) Whether the drug is a new molecular entity.

Id.

18. *Id.* § 355-1(a)(2)(A).

19. *Id.* § 355-1(c)–(d). Sponsors generally are required to conduct assessments within eighteen months after the REMS' approval, within three years after the approval, and within the seventh year after the approval. *Id.*; *see also* Masoudi, *supra* note 5, at 587 (noting that all REMS must include a timetable for assessing the plan's performance, and that this is the only required element).

20. *See* 21 U.S.C. § 355-1(e)–(f) (providing FDA with the discretionary authority to require additional elements in an REMS, including medication guides, communication plans, and elements to assure safe use); Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 512 (2010) (noting that some of the additional REMS elements are “simple, familiar measures FDA already has been using,” but that others are “more draconian”).

pursuant to 21 C.F.R. Part 208.²¹ In the middle of the scale, FDA may mandate other communication elements, such a patient package insert or letters to health care providers.²² At the more onerous end of the scale are so-called *elements to assure safe use* (ETASU).²³ These can include: training or certification for those who prescribe or dispense the drug, limiting the settings in which the drug can be dispensed, requiring patients to provide documentation of laboratory test results, or requiring registration or monitoring of patients using the drug.²⁴

B. Implementation of REMS

FDA approved the first new REMS²⁵—for Treximet (sumatriptan succinate and naproxen sodium) Tablets—on April 15, 2008.²⁶ Since then, FDA has

21. 21 U.S.C. § 355-1(e)(2)(A); 21 C.F.R. § 208.20 (2009). Medication guides are paper handouts that are provided with prescription medications. U.S. Food & Drug Admin., Medication Guides, <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm> (last visited May 17, 2010). “The guides address issues . . . specific to particular drugs and drug classes, and they contain FDA-approved information . . . [designed] to help patients avoid serious adverse events.” *Id.*

22. 21 U.S.C. § 355-1(e)(2)(B).

23. *Id.* § 355-1(f)(3).

24. *Id.* FDA may impose ETASU for a new drug where the agency determines that the drug (1) has been shown to be effective, but (2) is associated with a “serious adverse drug experience,” and (3) “can be approved only if . . . such elements are required . . . to mitigate a specific serious risk listed in the [drug] labeling . . .” *Id.* § 355-1(f)(1)(A). For an approved drug, the agency must find that the drug would be withdrawn unless ETASU are imposed and that other REMS elements are not sufficient to mitigate the serious risk at issue. *Id.* ETASU must “be commensurate with the specific serious risk listed in the labeling of the drug,” must “not be unduly burdensome on patient access to the drug,” and must, “to the extent practicable, . . . minimize the burden on the health care delivery system . . .” *Id.* § 355-1(f)(2)(A), (C)–(D).

On December 22, 2009, Kaiser Permanente (Kaiser), the largest private integrated health care delivery system in the United States, submitted a citizen petition to the FDA under 21 C.F.R. § 10.30 requesting that the agency revise its standards for the development, implementation, and evaluation of REMS. Citizen Petition of Benjamin Chu et al., Kaiser Permanente, FDA Dkt. No. FDA-2009-P-0602 (Dec. 22, 2009), available at <http://www.regulations.gov/search/Regs/contentStreamer?objectId=0900006480a71ffa&disposition=attachment&contentType=pdf> [hereinafter Citizen Petition of Chu et al.]. Kaiser’s Citizen Petition focuses in large part on ETASU, and requests that the agency: (1) “[i]ncrease the transparency and opportunity for comment by health care providers and . . . the public in the development process for REMS” involving ETASU; (2) make summary data collected as a result of REMS publicly available; (3) evaluate ETASU regularly to assess their effectiveness and include health care providers in that process; (4) ensure REMS are not used by drug companies to give preference to particular health care providers such as specialty pharmacies; and (5) take steps to guard the confidentiality of Protected Health Information disclosed as a result of REMS. *Id.* at 1–2.

25. Drugs approved before FDAAA’s effective date were deemed to have an approved REMS in effect if certain conditions were met. See Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313, 16,313 (Mar. 27, 2008) (indicating that certain drugs approved prior to FDAAA, which were effectively subject to ETASU, were deemed to have a REMS, requiring manufacturers to submit a proposed REMS to FDA). On March 27, 2008, the FDA published a Notice identifying sixteen drug and biological products deemed to have a REMS. *Id.* at 16,314 tbl.1.

approved REMS for a wide range of drugs across a variety of therapeutic areas.²⁷ Indeed, the agency required a REMS for one-third of new molecular entities approved in the first six months of its REMS authority.²⁸ Moreover, the agency appears to have approved REMS at an increasing pace: it approved twenty-five new REMS or modifications between April and December 2008, and more than triple that number—seventy-four—between January and December 8, 2009.²⁹ While it is unclear whether Congress intended REMS to be required sparingly, it appears that FDA views REMS as a powerful tool to help the agency better understand a product's use in the marketplace and is imposing REMS liberally as a result.

Of the REMS and modifications approved to date, the vast majority—eighty-four—include only a medication guide.³⁰ Twenty-four also include a communication plan,³¹ while thirteen involve ETASU and/or an implementation system.³² In addition, while FDA initially only approved REMS that were specific to an individual drug or biologic,³³ the agency more recently has required REMS for classes of drug products.³⁴ The agency has implemented class-wide REMS for botulinum toxin-based products, testosterone gel products, and erythropoiesis-

26. See U.S. Food & Drug Admin., Approved Risk Evaluation and Mitigation Strategies (REMS), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm> (last visited May 17, 2010) (providing a list of approved REMS).

27. See *id.* (listing the numerous drugs with FDA-approved REMS); Evans, *supra* note 20, at 514 (discussing the various drugs subject to REMS, including those with abuse or addiction potential, or drugs with grave use-risks, such as birth defects or irreversible organ damage).

28. Lauren Smith, *The REMS Report Card: FDA Using New Tools for One-Third of New Drugs in First Six Months*, THE PINK SHEET, Nov. 10, 2008.

29. U.S. Food & Drug Admin., *supra* note 26. Between January and April 2010, FDA has approved twenty-two new REMS. *Id.*

30. *Id.*

31. *Id.*

32. *Id.* As of May 17, 2010, FDA's list of approved REMS includes 121 separate products and identifies the elements associated with each REMS. *Id.* The approval dates included in the list, however, indicate that the agency has approved a total of 154 new REMS and/or modifications to existing REMS. *Id.*

33. See Evans, *supra* note 20, at 513–15 (discussing the initial REMS approvals granted by the FDA and indicating that the specific drug and biologic products were approved on a case-by-case basis).

34. See Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting, 74 Fed. Reg. 17,967, 17,969 (Apr. 20, 2009) (providing notice of a public meeting to discuss the development of REMS for classes of certain opioid drugs); CTR. FOR LAWFUL ACCESS & ABUSE DETERRENCE, A REVIEW OF THE FDA'S APPROACH TO IMPLEMENTING A CLASS-WIDE REMS FOR LONG-ACTING AND EXTENDED-RELEASE OPIOIDS 1, 3–4 (2010), available at <http://claad.org/downloads/REMS%20-%20FDA%20Approach%20Critique%20Final.pdf> (noting that the FDA has exercised its new authority to require certain producer of opioid drugs to propose a “class-wide, one-size-fits-all REMS,” and suggesting that the April 2009 meeting called by the FDA to discuss these proposals indicates that the FDA has “erroneously invoked the provisions Congress intended to guide assessments of individual drugs’ existing REMS”); Ravi Deshpande, *REMS Programs: Five Trends to Watch*, REG. POL’Y MARKET ACCESS REP., Aug. 2009, at 1, 2, available at http://www.mckesson.com/static_files/McKesson.com/McKSpecialty/PDFs/REMS0908rpm_SiteLicense.pdf (discussing the arguments for and against class-wide REMS).

stimulating agents,³⁵ and is in the process of developing a class-wide REMS for extended-release oral opioid drug products.³⁶

C. Draft REMS Guidance

In September 2009, FDA issued a Draft Guidance for Industry entitled “Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications” (Draft REMS Guidance).³⁷ The Draft REMS Guidance addresses the format and content of the proposed REMS and REMS supporting document,³⁸ and requires copies of all documents relevant to REMS elements (such as medication guides and patient package inserts) to be appended to the proposed REMS.³⁹ The Draft REMS Guidance also offers detailed instructions on submitting modifications to approved REMS and explicitly requires that:

Any proposed modification to [an] approved REMS, including any proposed changes to materials that are included as part of the REMS (e.g., communication and education materials, enrollment forms, prescriber and patient agreements), must be submitted as a proposed modification to an approved REMS in a new prior-approval

35. Press Release, U.S. Food & Drug Admin., FDA Announces New Safety Plan for Agents Used to Treat Chemotherapy-Related Anemia (Feb. 16, 2010), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm200471.htm>; Press Release, U.S. Food & Drug Admin., Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide (May 7, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm>; Press Release, U.S. Food & Drug Admin., FDA Requires Boxed Warning for All Botulinum Toxin Products (Apr. 30, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149574.htm>.

36. The agency has held a series of public and private meetings related to this proposed REMS. See Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting, 74 Fed. Reg. at 17,968–69 (discussing efforts to address the risks of opioid use via REMS); Press Release, U.S. Food & Drug Admin., Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS), available at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm> (last visited May 17, 2010) (documenting the various meetings to discuss the use of REMS for opioids). As noted in Kaiser’s Citizen Petition, although Section 505-1 of the FD&C Act requires FDA to obtain “input from patients, physicians, pharmacists and other health care providers about how the elements to assure safe use . . . for 1 or more drugs may be standardized so as not to be . . . unduly burdensome on patient access to the drug,” the proposed opioid REMS is the first for which the agency has sought public input. See Citizen Petition of Chu et al., *supra* note 24, at 3.

37. U.S. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS), REMS ASSESSMENTS, AND PROPOSED REMS MODIFICATIONS DRAFT GUIDANCE (2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> [hereinafter DRAFT REMS GUIDANCE].

38. *Id.* at 1. According to FDA, the proposed REMS is “a concise document that describes the proposed goals and elements of the REMS” while the REMS supporting document “expands on information included in the proposed REMS and provides additional information not included in the proposed REMS . . .” *Id.* at 7.

39. *Id.* at 8, 10.

supplemental application . . . and must not be implemented until the modified REMS is approved by FDA.⁴⁰

II. DISCUSSION

A REMS does not spring into existence. Rather, when FDA orders a sponsor to propose a REMS, the company faces a number of significant challenges in developing it, getting FDA approval, putting the REMS into practice and maintaining it. In addition to these challenges, however, the REMS process offers drug manufacturers substantial opportunities, which should not be—and have not been—overlooked. Moreover, the REMS process may give rise to specific challenges and opportunities with respect to potential state tort litigation. Perhaps most notably, it is possible that a REMS will serve to preempt certain state tort law failure-to-warn claims, although the likelihood and scope of such preemption is unclear in light of the Supreme Court’s recent decision in *Wyeth*. The discussion below first addresses certain challenges and opportunities specific to tort litigation,⁴¹ before turning to some of the more general challenges and opportunities that companies may encounter while operating under a REMS.⁴²

A. Tort Liability

1. Preemption

A potential benefit for manufacturers with a product subject to a REMS is that actions taken under the REMS, which require prior approval by FDA,⁴³ may preempt state law failure-to-warn claims. In 2006, the FDA issued a rule regarding the requirements for human prescription drug and biologics labeling, the Preamble to which clearly expressed the agency’s view that FDA labeling approval preempted conflicting or contrary state law.⁴⁴ In particular, the agency warned that state tort actions “encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA,” and could “pressure . . . manufacturers . . . to add

40. *Id.* at 22.

41. *See infra* Part II.A.

42. *See infra* Parts II.B–C.

43. *See supra* Part I.A.

44. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3922, 3934 (Jan. 24, 2006) (effective date June 30, 2006) [hereinafter FDA Preamble]; Victor E. Schwartz et al., *Marketing Pharmaceutical Products in the Twenty-First Century: An Analysis of the Continued Viability of Traditional Principles of Law in the Age of Direct-to-Consumer Advertising*, 32 HARV. J.L. & PUB. POL’Y 333, 380 (2009). The FDA Preamble stressed that “FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading.” FDA Preamble, *supra*, at 3934.

warnings that FDA has neither approved nor found to be scientifically required.”⁴⁵ Although the agency acknowledged that its regulation of drug labeling would not preempt all state tort actions,⁴⁶ FDA identified six types of claims that it believed would be preempted by its regulation of prescription drug labeling.⁴⁷

The Supreme Court specifically considered the FDA Preamble in *Wyeth*, en route to concluding that Wyeth had not demonstrated a sufficient conflict between state and federal regulation to establish a preemption defense against a state tort law failure-to-warn claim.⁴⁸ Diana Levine, the *Wyeth* plaintiff, received an incorrect IV-push administration of an anti-nausea drug manufactured by Wyeth, which caused gangrene and the eventual amputation of her forearm.⁴⁹ “Although [the drug]’s labeling warned of the danger of gangrene and amputation following inadvertent intra-arterial injection, Levine [nevertheless] alleged that the labeling was defective because it failed to instruct clinicians to use the IV-drip method of intravenous administration instead of the higher risk IV-push method.”⁵⁰ Levine was awarded a \$7.4 million jury verdict, which the trial court refused to overturn on preemption grounds, and which the Vermont Supreme Court affirmed.⁵¹

The Supreme Court’s opinion in *Wyeth* rejected two preemption arguments advanced by Wyeth: first, “that it would have been impossible for [the company] to comply with the state-law duty to modify [the drug]’s labeling without violating federal law,” and second, “that requiring [the company] to comply with a state-law duty to provide a stronger warning about IV-push administration would obstruct the purposes and objectives of federal drug labeling regulation.”⁵² As to the first argument, the Court found that, while manufacturers generally are required to obtain FDA approval of a supplemental application before changing a drug label, FDA’s “changes being effected” (CBE) regulation permits a manufacturer to “add or strengthen a contraindication, warning, precaution, or adverse reaction” or “an instruction about dosage and administration that is intended to increase the safe use of the drug product . . . upon filing its supplemental application with the FDA”⁵³ As to those categories of information, a manufacturer “need not wait for FDA approval” before changing a drug label, and the Court therefore concluded

45. FDA Preamble, *supra* note 44, at 3935.

46. *Id.* at 3936.

47. *Id.* at 3935–36. In particular, the agency acknowledged that “[t]he Supreme Court has held that certain State law requirements that parallel FDA requirements may not be preempted.” *Id.* at 3936 (citing *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996)).

48. See 129 S. Ct. 1187, 1200–02, 1204 (2009) (noting that the FDA Preamble “is at odds with . . . Congress’ purposes, and it reverses the FDA’s own longstanding position without providing a reasonable explanation”).

49. *Id.* at 1191.

50. *Id.* at 1191–92.

51. *Id.* at 1193.

52. *Id.* at 1193, 1199.

53. *Id.* at 1196 (quoting 21 C.F.R. §§ 314.70(c)(6)(iii)(A), (C)) (internal quotations omitted).

that Wyeth would, at least in theory, have been permitted to strengthen its label to warn about the dangers of IV-push administration.⁵⁴ The Court further found that Wyeth had not provided “clear evidence that the FDA would not have approved a change to the . . . label” and therefore had not demonstrated “that it was impossible . . . to comply with both federal and state requirements.”⁵⁵

Wyeth’s second preemption argument—that recognizing Levine’s state tort action would interfere with federal regulation of drug labeling—relied in part upon the FDA Preamble.⁵⁶ In addressing Wyeth’s second argument, the Court first observed:

If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express preemption provision at some point during the [FD&C Act]’s 70-year history. But despite its 1976 enactment of an express pre-emption provision for medical devices, Congress has not enacted such a provision for prescription drugs.⁵⁷

The Court then turned to the FDA Preamble, and in particular, its position that the FD&C Act establishes “both a ‘floor’ and a ‘ceiling’” that prevents manufacturers from including unsubstantiated risk information on drug labels.⁵⁸ The Court found the FDA Preamble did not merit deference because it “relie[d] on an untenable interpretation of congressional intent and an overbroad view of an agency’s power to pre-empt state law.”⁵⁹ Specifically, the Court observed that because “FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation[, t]he agency’s 2006 preamble represents a dramatic change in position.”⁶⁰

While *Wyeth* concluded that FDA regulation did not preempt a state tort law failure-to-warn claim, it did so in the very specific context of, and relied heavily upon, the CBE regulation.⁶¹ In stark contrast to the CBE regulation, however, the FDA’s recent Draft REMS Guidance makes clear that (1) *any* proposed modification to an approved REMS—or the tools implementing it—“must be submitted . . . in a new prior-approval supplemental application,” and (2) proposed modifications “must not be implemented until the modified REMS is approved by FDA.”⁶² These key distinctions may well prove significant to the potential viability of a preemption defense based on a REMS because, unlike in *Wyeth*, a drug manufacturer operating under a REMS cannot add additional warnings to its REMS

54. *Id.*

55. *Id.* at 1198–99.

56. *Id.* at 1200–01.

57. *Id.* at 1200 (citation omitted).

58. *Id.* (quoting FDA Preamble, *supra* note 44, at 3935).

59. *Id.* at 1199.

60. *Id.* at 1202–03.

61. *Id.* at 1199, 1204.

62. DRAFT REMS GUIDANCE, *supra* note 37, at 22.

materials without explicit pre-approval by FDA. Rather, a manufacturer may be able to successfully defend against a state tort failure-to-warn claim based upon a REMS by arguing that it is impossible to comply with both FDA's interpretation of its REMS authority and state law duties that would require additional warnings.⁶³ For the same reason, a preemption defense may be available where a drug label specifically refers to REMS materials for their discussion of a specific risk.⁶⁴

In many respects, a preemption defense premised on the presence of a REMS is perfectly intuitive. Notably, FDA may require a REMS where it concludes that one "is necessary to ensure that the benefits of the drug outweigh the risks of the drug" after considering certain factors.⁶⁵ FDA then requires the drug sponsor to propose a REMS and all of the implementing tools (e.g., communication materials), works with the sponsor to ensure that the REMS properly describes the risk at issue and provides appropriate safety information, and eventually approves the REMS.⁶⁶ Through these processes, FDA squarely focuses on the risk in question and strikes what it considers to be an appropriate balance with respect to risk information. So too, the REMS process is likely to generate a substantial administrative record demonstrating FDA's consideration of the specific risk and, perhaps, the agency's rationale in approving the ultimate balance reflected in the REMS. A lack of this type of agency focus—and corresponding administrative record—was one of the very factors the Court found weighed against preemption in *Wyeth*.⁶⁷ As such, evidence of agency focus, demonstrated through an administrative record, may bolster the argument for preemption based upon a REMS.

2. Litigation Risks and Strategy

Aside from the open question of whether a REMS may give rise to a preemption defense against state tort law failure-to-warn claims, REMS may create additional challenges and opportunities for manufacturers with respect to tort liability. Most obviously, a REMS is likely to lead to increased visibility regarding

63. Cf. *Wyeth*, 129 S. Ct. at 1198–99 (implying that had the company not been able to comply with both laws the state claim would have been preempted).

64. Indeed, given the opposing requirements of the CBE regulation and Draft REMS Guidance, a manufacturer may find itself in the position of adding risk information to its label that it may not include in its REMS because it has not yet been approved by FDA. This would certainly be ironic since the REMS is supposed to serve as the primary mechanism for communicating risk information.

65. 21 U.S.C. § 355-1(a)(1) (West Supp. 2009); see *supra* note 17.

66. § 355-1(a)(1), (h)(1).

67. See *Wyeth*, 129 S.Ct. at 1198–99 (“[W]hile [Wyeth] does suggest that the FDA intended to prohibit it from strengthening the warning about IV-push administration because the agency deemed such a warning inappropriate in reviewing [the drug]’s . . . applications, both the trial court and the Vermont Supreme Court rejected this account as a matter of fact. In its decision on Wyeth’s motion for judgment as a matter of law, the trial court found ‘no evidence in th[e] record that either the FDA or the manufacturer gave more than passing attention to the issue of IV-push versus IV-drip administration.’”).

a drug's safety profile.⁶⁸ Although all drugs have inherent safety risks, and FDA can only approve a REMS "to ensure that the benefits . . . outweigh the risks" of an otherwise safe and effective drug,⁶⁹ a REMS essentially spotlights safety issues for potential plaintiffs. Such a spotlight may be particularly damaging if only one drug in a class is subject to a REMS, insofar as plaintiffs may argue that they would have used alternative therapies if the drug's REMS had provided other risk information. Moreover, the REMS process—which, as discussed above, may lead to the creation of an administrative record useful for preemption purposes—also may lead to the creation of documents that highlight the risks at issue or could otherwise be used to cast a manufacturer in a negative light during litigation.

On the other hand, a REMS may play a key role in a drug manufacturer's efforts to avoid tort litigation altogether, or may better position a manufacturer in event of litigation. As discussed below, a REMS may offer a manufacturer increased opportunities to communicate important safety information to health care providers and patients before a drug is used.⁷⁰ In this way, a REMS may ensure safe use in the first instance, such as by requiring laboratory testing for key risk factors, and thereby avoid future tort claims.⁷¹ The REMS process also may afford a manufacturer the chance to demonstrate its commitment to working cooperatively with FDA. Thus, documents created during the REMS process may portray the manufacturer in a positive light and may be helpful in defending against tort litigation. And, in the most dramatic instance, a REMS may constitute a strong defense against a state tort law failure-to-warn claim because it is specifically designed—and approved by FDA—to provide appropriate risk information to relevant health care provider and patient populations.

B. Challenges

In addition to raising specific issues with respect to tort liability, REMS and the REMS development, implementation, and maintenance processes present a host of other challenges and opportunities, which manufacturers and FDA are only beginning to navigate. Perhaps most obviously, the process of proposing and implementing a REMS can involve substantial costs, financial and otherwise. For instance, the financial costs involved in designing and implementing a REMS may

68. See § 355-1(h)(3)(C) (requiring that action letters and orders addressing risk evaluation and management strategies be publicly available); Masoudi, *supra* note 5, at 587 (noting that FDA can require dissemination of communications including certain REMS protocols).

69. § 355-1(a)(1).

70. See *infra* Part II.C.

71. See Christof A. Marré & Peggy Berry, *Designing a Safety Risk Management Strategy*, REG. FOCUS, Nov. 2008, at 20, 21–25 (discussing how REMS impact the medical industry's role in providing a higher level of care to patients); Eli Lilly & Co., Risk Evaluation and Mitigation Strategies (REMS): What Does a REMS Look Like?, <http://safetymatters.lilly.com/rolelilly/riskEvalMitigationPlan.htm> (last visited May 17, 2010) (stating that some REMS require special procedures, such as mandatory laboratory tests, to be administered before a REMS product is issued to a patient).

include preparing communication tools such as *Dear Health Care Provider Letters*, establishing training and certification systems, creating monitoring and registry systems, and designing limited dispensing procedures.⁷² While these costs are unlikely to be entirely avoidable, a sponsor may be able to minimize some of them if it can anticipate that FDA may require a REMS for its drug, perhaps because REMS have been required for other drugs in a class. Such anticipation may allow a sponsor to handle projects internally that would otherwise need to be outsourced, and also may allow a company to avoid an otherwise likely delay in product launch.

Once a REMS is designed, proposed, and approved, the sponsor faces additional financial costs in maintaining the REMS, such as performing the assessments required by the REMS statute.⁷³ Sponsors also may propose modifications to an approved REMS at any time⁷⁴ and, as the Draft REMS Guidance makes clear, any proposed modification to a REMS—or the tools implementing the approved REMS—must be submitted in a new prior-approval supplemental application.⁷⁵ Given their respective complexities, preparing REMS assessments and REMS supplemental applications both are likely to involve substantial financial costs for REMS sponsors.

In addition to financial costs, operating under a REMS may impose certain commercial costs on a manufacturer as well. As a fundamental matter, a highly restrictive REMS, such as one that limits the settings in which a drug may be dispensed, may impact significantly the volume of a drug that can be distributed. Such limitations on availability may make health care providers less likely to prescribe a particular drug, especially if an equally effective alternative therapy is available.⁷⁶ Health care providers also may be more reluctant to prescribe or

72. See Alan Minsk & Lanchi Nguyen, *REMS, Risk and Reward*, LJM'S PROD. LIAB. L. & STRATEGY NEWSLETTER (Incisive Media, New York, N.Y.), Oct. 2009, at 7, 7 (discussing the benefits and risks of REMS implementation).

73. As noted above, sponsors are generally required to assess a REMS' effectiveness three times within the seven years after its approval. See *supra* note 19. Sponsors also may voluntarily submit assessments at any time, and are required to submit an assessment 1) when submitting a supplemental application for a new indication for use, 2) when required by FDA if the agency determines that new safety or effectiveness information indicates that an element should be modified or included in the REMS, and 3) within fifteen days when ordered by FDA if the agency determines there may be cause for withdrawal or suspension of approval under Section 505(e) of the FD&C Act. DRAFT REMS GUIDANCE, *supra* note 37, at 6–7.

74. § 355-1(g)(4).

75. Per the Draft REMS Guidance, this supplemental application must include: (i) a new proposed REMS showing the complete previously approved REMS and highlighting the proposed modifications, and (ii) "an update to the REMS supporting document that includes the rationale for and description of all proposed modifications and any impact the proposed modifications would have on other REMS elements." DRAFT REMS GUIDANCE, *supra* note 37, at 22.

76. See Citizen Petition of Chu et al., *supra* note 24, at 7 ("In effect, [ETASU] create[] a separate category of drugs, which require considerably more labor in the health care delivery setting to satisfy REMS ETASU requirements and to provide the drug in the safest manner possible.").

dispense a certain drug if the REMS' ETASU require action—such as certification or training—on the part of such providers or require providers to engage in specific patient education prior to use.⁷⁷ In essence, any REMS element that requires additional effort on the part of health care providers is likely to adversely impact sales, at least where an alternative therapy is available.

A REMS that relates to a specific drug (as opposed to a class-wide REMS) also may involve notable competitive costs for the drug at issue. Even though FDA can only impose REMS on drugs and biologics that the agency otherwise finds to be safe and effective, the existence of a REMS may give health care providers or patients the impression that a specific drug or biologic presents higher safety risks than alternative therapies.⁷⁸ The drug with the REMS may suffer competitively, particularly where only one drug in a class has a REMS, or where a new drug with a REMS enters the market against already approved drugs that have similar risks but no REMS. Drug manufacturers are, of course, most interested in ensuring that important risk information about their products is communicated to appropriate patients in an effective manner.⁷⁹ Nevertheless, these significant financial, commercial, and competitive costs cannot be ignored by manufacturers.

Moreover, in addition to costs, a REMS involves a heightened level of complexity for a manufacturer. Even without a REMS in place, companies face significant administrative burdens in ensuring that drug labels reflect appropriate and up-to-date risk information, as required by the FD&C Act and FDA's implementing regulations. Maintaining a REMS likely will add another layer of complexity to such companies' operations, which in turn will increase the costs of compliance.

C. Opportunities

While operating under a REMS involves obvious burdens, there also seem to be a number of potential opportunities presented by the REMS process. For instance, the REMS proposal and approval process requires drug sponsors to focus on their product's risk profile earlier, with greater intensity and frequency.⁸⁰ While

77. See Citizen Petition of Chu et al., *supra* note 24, at 4 (“REMS with ETASU can substantially increase the workload burden and costs associated with the prescribing, dispensing, administration and management of certain drugs . . .”); Minsk & Nguyen, *supra* note 72, at 11 (“[M]echanisms required to ensure the safe use of the product can . . . [cause] a physician's reluctance to prescribe with restrictions or additional responsibilities.”).

78. Minsk & Nguyen, *supra* note 72, at 11.

79. Cf. PHARM. RESEARCH & MFRS. OF AM., PHRMA GUIDING PRINCIPLES: DIRECT TO CONSUMERS ADVERTISEMENTS ABOUT PRESCRIPTION MEDICINES 3 (2008), http://www.phrma.org/files/attachments/PhRMA%20Guiding%20Principles_Dec%202008_FINAL.pdf (“[Direct-to-consumer] communications . . . can be a powerful tool for reaching and educating millions of people, and [pharmaceutical manufacturers] are committed to ensuring that . . . [such] communications provide accurate, accessible and useful health information to patients and consumers.”).

80. Minsk & Nguyen, *supra* note 72, at 12.

this may appear to be a cost, it can in fact be an opportunity insofar as it gives a manufacturer some chance to minimize the risks involved in using its drug by providing accurate and effective information to health care providers and patients.⁸¹ Indeed, in certain instances where a significant risk exists, a REMS may offer the only means of providing patients with access to a drug, for instance through a restricted distribution system.⁸²

Moreover, a REMS that involves a communication plan creates notable opportunities to the extent that it affords a drug sponsor additional avenues through which to communicate with health care providers regarding a particular product. In addition to disseminating safety information through these channels, the sponsor may be able to garner important information about how the drug is used in practice, which may in turn inform the safety information the company seeks to disseminate. Of course, however, the restrictions that generally apply to manufacturers' communications with health care providers—such as the prohibition on off-label promotion by manufacturers⁸³—continue to apply in the context of REMS-mandated communications.

Finally, in addition to increased opportunities to communicate with health care providers and patients, the REMS approval process may provide sponsors with the chance for additional pre-approval interaction with the FDA. Ideally, this interaction would allow sponsors to gain increased understanding of FDA's views on the drug or biologic at issue, and might even lead to faster approvals.

CONCLUSION

In summary, while it remains to be seen what impact REMS will have on manufacturer tort liability, and while it is clear that developing, implementing, and maintaining a REMS will involve significant burdens for manufacturers, the

81. *Id.*

82. See Citizen Petition of Chu et al., *supra* note 24, at 7 (“By design, [S]ection 505-1(f) [of the FD&C Act] makes some drugs available that would otherwise not be dispensed outside of an investigational setting, expanding treatment options for patients.”).

83. See Wash. Legal Found. v. Henney, 202 F.3d 331, 332–33 (D.C. Cir. 2000) (“[I]t is unlawful for a manufacturer to introduce a drug into interstate commerce with an intent that it be used for an off-label purpose, and a manufacturer illegally ‘misbrands’ a drug if the drug’s labeling includes information about its unapproved uses.” (citing 21 U.S.C. §§ 331(a), (d), 352(a) (citations omitted)). By regulation, FDA has broadly defined *labeling* to include:

Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the “Physicians Desk Reference”) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor . . .

21 C.F.R. § 202.1(f)(2).

possibility also exists that FDA's new authority will, at least in some ways, prove beneficial for drug manufacturers.

