

AN ANALYSIS OF FDA’S DRUG SAFETY AUTHORITIES: CHALLENGES AND OPPORTUNITIES UNDER A NEW REGULATORY FRAMEWORK

Kevin M. Fain,* Keeve E. Nachman,** & Lainie Rutkow***

The U.S. Food and Drug Administration (FDA) is responsible for ensuring the safety and effectiveness of all prescription drugs marketed in the United States. Beginning in the late 1990s, significant examples of risks emerged for FDA-approved drugs that had not been identified in studies conducted for drug approval. The Food and Drug Administration Amendments Act of 2007 provided the FDA with greater legal authorities to address such safety risks, including requirements for labeling changes, post-approval studies, and Risk Evaluation and Mitigation Strategies (REMS) for new and already-marketed drugs. REMS can include information provided directly to patients or healthcare professionals, as well as conditions for restricted use. In this article, we analyze FDA’s implementation of its REMS authorities from March 2008 to March 2012, and offer recommendations in light of our findings.

INTRODUCTION	2
I. FDA’S REGULATORY RESPONSE TO AN INCREASE IN DRUG ADVERSE EVENTS	4
A. FDAAA Authorities for Drug Safety	10
B. FDA’s Implementation of REMS	13
II. A FOUR-YEAR ANALYSIS OF REMS EMPLOYED BY FDA.....	15
III. POLICY IMPLICATIONS OF FDA’S REMS IMPLEMENTATION	23

* DrPH candidate, Johns Hopkins Bloomberg School of Public Health; MPH, Johns Hopkins Bloomberg School of Public Health; JD, University of Chicago Law School; BA, Duke University. The research associated with this article was conducted to fulfill the requirements for Kevin Fain’s MPH Capstone project at the Johns Hopkins Bloomberg School of Public Health.

** Assistant Scientist and Director, Food Production and Public Health Program, Center for a Livable Future, Johns Hopkins Bloomberg School of Public Health; PhD, Johns Hopkins Bloomberg School of Public Health; MHS, Johns Hopkins Bloomberg School of Public Health; BA, Johns Hopkins University.

*** Assistant Professor and Assistant Director, Center for Law and the Public’s Health, Johns Hopkins Bloomberg School of Public Health; JD, New York University School of Law; PhD, Johns Hopkins Bloomberg School of Public Health; MPH, Johns Hopkins Bloomberg School of Public Health; BA, Yale University.

A.	FDA's Approach to Medication Guides under FDAAA	23
1.	FDA's Shift in Policy for Medication Guides	25
2.	Revisiting Drug Sponsors' Assessment Methods for REMS	27
B.	Limitations in the Publicly Available Data	28
1.	FDA's Position for Limiting Publicly Available REMS Information	30
2.	FDA's Approach to Sharing REMS Information for Avandia	33
	CONCLUSION	35

INTRODUCTION

Prescription drug safety is a critical public health concern for millions of Americans who take medications to treat and manage diseases. Under the Federal Food, Drug, and Cosmetic Act (FDC Act),¹ the U.S. Food and Drug Administration (FDA) is charged with the responsibility of ensuring that all prescription drugs are both safe and effective for patient use.² Before a prescription drug can legally be marketed to American consumers, the company that developed the drug (hereinafter the “drug sponsor”) must submit an application, including sufficient data and information to demonstrate the drug’s safety and effectiveness, for FDA’s review and approval.³ Under the FDC Act and its implementing regulations, FDA balances the risks and benefits in determining whether to approve, or later withdraw approval of, a prescription drug.⁴ The statute and regulations do not provide an explicit formula for drug safety analysis or a quantitative threshold for drug safety findings. FDA’s safety decisions are grounded in the individual context of each drug, such as the nature and

1. 21 U.S.C. §§ 301–399d (2012) (FDC Act).

2. *See* § 393(B)(2)(b). Prescription drugs under the FDC Act include traditional small molecule drugs and biologics for therapeutic use. A therapeutic biologic is derived from living material (such as cells or tissues) and used to treat or cure disease. Traditional small molecule drugs are generally manufactured by a chemical process, while therapeutic biologics are generally manufactured by a biological process. *See Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm> (last updated Dec. 24, 2009). In this article, the terms “prescription drug,” “drug product,” and “drug” are all used to refer to both small molecule drugs and biologics.

3. 21 U.S.C. § 355(b); *see* 21 C.F.R. § 314.50 (2013).

4. 21 U.S.C. § 355(b); *see* 21 C.F.R. § 314.50 (2013).

severity of the disease the drug will treat and the availability of alternative treatments.⁵

Under this regulatory framework, FDA approves a drug's use for specific indications that are supported by the submitted evidence. This evidence includes a series of clinical trials, conducted by the drug sponsor, over three "phases" to test the drug's safety and effectiveness for its indication(s).⁶ The most comprehensive trials, in phase III, are generally randomized clinical trials with control and treatment groups for comparison.⁷ FDA also approves the drug's labeling, which provides thorough information about the drug and its use, including chemistry, toxicology, clinical data, indications, and warnings.⁸ These descriptions are written for health care providers, such as physicians and pharmacists. This labeling accompanies the drug during distribution from the drug sponsor to the dispenser. Thus, pharmacists receive this information directly, but the federal government does not require the labeling to be provided to patients.⁹ Physicians access the labeling

5. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DEVELOPMENT AND USE OF RISK MINIMIZATION ACTION PLANS 4 (2005), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf> ("[A]ssessment and comparison of a product's benefits and risks is a complicated process that is influenced by a wide range of societal, healthcare, and individualized patient factors.").

6. 21 C.F.R. § 312.21 (2013).

7. A clinical trial is a research study conducted by an investigator to assess a drug's safety and effectiveness under controlled conditions. By a process known as "randomization," research subjects are randomly assigned to a treatment group (receiving the intervention) and a comparison group or groups (receiving a placebo or other intervention). Each group's disease and/or health outcomes are measured by the investigators. There are typically three clinical trial phases for FDA's approval of a prescription drug:

[I]n Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety and identify side effects. In Phase II trials, the experimental drug or treatment is administered to a larger group of people (100-300) to determine its effectiveness and to further evaluate its safety. In Phase III trials, the experimental drug or treatment is administered to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it with standard or equivalent treatments, and collect information that will allow the experimental drug or treatment to be used safely.

Clinical Research Trials and You: The Basics, NAT'L INSTS. HEALTH, <http://www.nih.gov/health/clinicaltrials/basics.htm#1> (last visited Jan. 25, 2014). In a so-called "Phase IV trial," after the drug is approved by the FDA and is manufactured and prescribed to patients, researchers continue to track its safety and seek more information about the drug or treatment risk, benefits, and optimal use. *Id.*

8. 21 C.F.R. §§ 201.56, 201.57, 314.50(e), 314.105.

9. 21 U.S.C. §§ 352(f)(1), 353(b)(1); 21 C.F.R. §§ 201.56, 201.57, 201.100. 21 U.S.C. § 353(b)(1) and 21 C.F.R. §§ 201.56 and 201.57 require thorough summaries of scientific information to be included in the drug labeling for health care professionals, such as descriptions of the drug studies reviewed by FDA; but 21 U.S.C. § 353(b)(1) and 21 C.F.R. § 201.100 exempt the prescription drug from these labeling

information through professional publications such as the *Physicians' Desk Reference*,¹⁰ or through the FDA and National Library of Medicine websites.¹¹ Under this regulatory framework, physicians and pharmacists act as learned intermediaries for patients in reviewing labeling information and use professional judgment in prescribing and dispensing drugs.

The legal framework for assuring prescription drug safety and effectiveness was updated in the Food and Drug Administration Amendments Act of 2007 (FDAAA),¹² which granted FDA significant new authorities. This article examines FDA's implementation of these new prescription drug safety authorities, including the use of Risk Evaluation and Mitigation Strategies (REMS). Part I describes how FDA regulated prescription drug safety before FDAAA's enactment. It also explains the new REMS authorities granted by FDAAA and how FDA has implemented these statutory REMS provisions during the four years since the law's effective date of March 25, 2008. Part II presents our analysis of REMS required by FDA, as well as those REMS subsequently released (*i.e.*, no longer required) by the agency, from 2008 to 2012. This Part describes variations in the types of REMS as well as the risks and evidence supporting them. Part III examines important policy concerns related to FDA's implementation of its REMS authorities and offers recommendations in light of these challenges. Finally, Part IV summarizes the article's findings and conclusions.

I.

FDA'S REGULATORY RESPONSE TO AN INCREASE IN DRUG ADVERSE EVENTS

Beginning in the late 1990s through the present, there have been highly publicized instances of FDA-approved drugs causing significant adverse events that were not seen in the clinical trials conducted for drug approval.¹³ Clinical trials are typically conducted over a lim-

requirements when dispensed to patients, as long as certain minimal information is included, such as the "Rx" designation and dosage amount.

10. PDR NETWORK, *PHYSICIANS' DESK REFERENCE* (66th ed. 2012).

11. *About DailyMed*, DAILYMED, <http://dailymed.nlm.nih.gov/dailymed/about.cfm?CFID=73190631> (last visited Jan. 25, 2014); *Drugs@FDA: FDA Approved Drug Products*, U.S. FOOD & DRUG ADMIN., <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?CFID=56261304> (last visited Jan. 25, 2014).

12. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007).

13. *See, e.g.*, U.S. GOV'T ACCOUNTABILITY OFFICE, *DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 1-2* (2006) ("In 2004, several high-profile drug safety cases raised concerns about the

ited period of time and with limited numbers of subjects.¹⁴ As some drugs were used by greater numbers of patients over longer periods of time, certain adverse events (referred to as safety “signals” when observed in drug safety surveillance) began to be reported. Several drugs were subsequently withdrawn voluntarily by the drug sponsor, including the weight loss drug Fen-Phen in 1997 because of heart valve risk;¹⁵ the diabetes drug Rezulin in 2000 because of hepatotoxicity risk;¹⁶ the statin drug Baycol in 2001 because of rhabdomyolysis risk;¹⁷ and the non-steroidal anti-inflammatory drug Vioxx in 2004 because of myocardial infarction risk.¹⁸

In response to the increasing frequency of adverse events associated with these and other pharmaceuticals, FDA developed and expanded three administrative mechanisms for ensuring the safer use of drugs that posed greater risks. FDA focused on providing safety information directly to patients and doctors, as well as imposing additional conditions on the prescribing and dispensing of drugs to ensure safer use by patients.¹⁹ By preventing additional cases of newly observed adverse events, these administrative mechanisms could allow a drug to remain on the market.

In 1998, FDA began to require by regulation that drug sponsors provide “Medication Guides” directly to patients at the time of dispensing for certain drugs.²⁰ Medication Guides are intended to inform

Food and Drug Administration’s . . . management of safety issues concerning drugs that have been approved for marketing.”).

14. NAT’L INSTS. HEALTH, *supra* note 7.

15. Press Release, U.S. Food & Drug Admin., FDA Announces Withdrawal of Fenfluramine and Dexfenfluramine (Fen-Phen) (Sept. 15, 1997), *available at* <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm179871.htm>.

16. Press Release, U.S. Food & Drug Admin., Rezulin to be Withdrawn from the Market (Mar. 21, 2000), *available at* http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3634b1a_tab6c.htm (hepatotoxicity involves a destructive effect on the liver).

17. *Baycol (cerivastatin sodium tablets)*, U.S. FOOD & DRUG ADMIN., (Aug. 8, 2001), <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172268.htm>. Rhabdomyolysis involves the disintegration of striated muscle fibers and the excretion of myoglobin in the urine. Rhabdomyolysis, MEDLINE PLUS, <http://www.nlm.nih.gov/medlineplus/ency/article/000473.htm>.

18. *Vioxx (rofecoxib) Questions and Answers*, U.S. FOOD & DRUG ADMIN., (Sept. 30, 2004), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106290.htm>.

19. Deborah B. Leiderman, *Risk Management of Drug Products and the U.S. Food and Drug Administration: Evolution and Context*, 105S DRUG & ALCOHOL DEPENDENCE S10–S12 (2009).

20. Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66,396 (Dec. 1, 1998) (codified in scattered sections of 21 C.F.R.).

patients of the serious safety risks associated with a drug's use.²¹ This step provides an additional pathway by which patients are informed of risks, rather than solely through the doctor-patient relationship. Under the regulation, a Medication Guide is required when additional information could help prevent adverse effects,²² when the information about serious risks could affect individuals' decision to use the drug,²³ or when adherence to directions for use is critical.²⁴ Before 2007, the FDC Act did not specify Medication Guides as a possible condition for drug approval or continued marketing.²⁵

21. 21 C.F.R. § 208.1(a) (2013).

22. 21 C.F.R. § 208.1(c)(1) (2013). For example, FDA required a Medication Guide for Botox (botulinum toxin) products in 2009 and justified the requirement under 21 C.F.R. § 208.1(c)(1). FDA explained that additional information for patients about adverse effects—such as problems with swallowing, speaking, or breathing—would help patients self-monitor for these events and increase the likelihood of earlier medical intervention, including monitoring and treatment. In this way FDA believed the Medication Guide would help prevent adverse events and their consequences. Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Research, U.S. Food & Drug Admin., to Pub. Citizen Health Research Group 16–17 (Apr. 30, 2009), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/UCM143989.pdf>.

23. 21 C.F.R. § 208.1(c)(2). In FDA's justification for the Medication Guide final rule, the Agency explained those circumstances where patients might not choose to use a drug when informed of the adverse effects. FDA stated this condition would apply where a drug's risk is "greater than a patient would anticipate given the relatively benign condition being treated (e.g., isotretinoin is used to treat acne, not usually considered a seriously morbid condition, but the drug can cause severe birth defects in an exposed fetus)" Prescription Drug Product Labeling; Medication Guide Requirements; Final Rule, 63 Fed. Reg. 66,378, 66,388 (Dec. 1, 1998) (codified in scattered sections of 21 C.F.R.). FDA also explained this condition would apply "where understanding the adverse effects is critical to a choice among alternative treatments with different safety and effectiveness profiles (e.g., choice of barrier contraception versus oral, injectable, or implantable birth control)" *Id.* Finally, FDA explained this condition would apply "where there is an important relation of duration of use to risk (e.g., increased risk of endometrial cancer with chronic administration of oral estrogens, or increased risk of habituation with prolonged use of benzodiazepine hypnotics)." *Id.*

24. 21 C.F.R. § 208.1(c)(3). In FDA's justification for the Medication Guide final rule, the Agency explained circumstances when patient adherence to the drug's approved directions could be critical for the drug's effectiveness. FDA stated this condition would apply:

where nonadherence could compromise patients' health by interfering with effectiveness; e.g., labeling could remind people that taking alendronate sodium at least one-half hour before the first food, beverage, or medication of the day with plain water only (other beverages, food, and some medications are likely to reduce the absorption of alendronate), is essential to the drug's effectiveness in treating osteoporosis.

Prescription Drug Product Labeling, Medication Guide Requirements, 63 Fed. Reg. at 66,388.

25. *See* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–399 (2012).

Second, FDA could request that drug sponsors send “Dear Health Care Professional” letters to physicians describing a significant health hazard associated with a particular drug.²⁶ FDA could also draft and post separate “Healthcare Professional Sheets,” which it makes available on its website, with specific information for physicians describing a drug’s safety risks.²⁷ These letters and sheets could be particularly important for new safety signals about which physicians might be unaware; even though the drug’s labeling would be updated, a communication directly to physicians would provide greater assurance of their awareness of the new information. Before 2007, the FDC Act did not provide explicit authority for FDA to require drug sponsors to send such letters.²⁸

Third, FDA developed Risk Minimization Action Plans (RiskMAPs), initially described in a 2005 agency guidance.²⁹ The guidance described the different RiskMAP elements, which could include Medication Guides, communication plans to health care professionals, and restricted distribution conditions, such as physician and patient education and certification programs and prescription tracking.³⁰ These more restrictive elements were important because FDA found in some cases that communications to patients and doctors, as well as labeling changes, were insufficient by themselves to prevent certain harms.³¹

For example, Lotronex was approved in February 2000 to treat irritable bowel syndrome in women, but FDA soon afterward began receiving adverse event reports—including death—associated with the drug’s use.³² At FDA’s request, the company that manufactured Lotronex issued a Medication Guide to patients and a letter to physicians and pharmacists with this risk information. Despite these communica-

26. OFFICE OF NEW DRUGS, CTR. FOR DRUG EVAL. & RESEARCH, NDAs: “DEAR HEALTH CARE PROFESSIONAL” LETTERS 1–2 (2003), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082012.pdf>.

27. See Healthcare Professional Sheets, U.S. Food & Drug Admin., *Healthcare Professional Sheets*, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm081890.htm> (last visited Jan. 27, 2014).

28. See 21 U.S.C. §§ 301–399.

29. See U.S. FOOD & DRUG ADMIN., *supra* note 5, at 8–12.

30. *Id.*

31. Am. Pharmacists Ass’n, *White Paper on Designing a Risk Evaluation and Mitigation Strategies (REMS) System to Optimize the Balance of Patient Access, Medication Safety, and Impact on the Health Care System*, 49 J. AM. PHARMACISTS ASS’N 729, 731 (2009) (describing instances in which communications alone did not effectively address adverse event prevention).

32. *Id.*

tion steps, serious adverse events continued to be reported. After being withdrawn from the market, Lotronex was reintroduced in June 2002 under a restricted distribution plan to better ensure patient safety.³³ Among other conditions, physicians enrolled in the restricted distribution program “must attest to having certain qualifications and agree to fulfill specific responsibilities,” such as having patients sign a “Patient-Physician Agreement indicating that they understand the risks and benefits of Lotronex.”³⁴

By February 2007, there were thirty RiskMAPs that varied in scope.³⁵ The plans and conditions, however, were voluntary because the FDC Act at that time did not grant explicit authority for FDA to impose RiskMAP conditions for a drug’s approval. Therefore, FDA’s guidance elements were only recommendations.³⁶ FDA could not enforce a drug sponsor’s adherence to a RiskMAP as a required condition for marketing.³⁷

FDA pursued these three administrative options (*i.e.*, Medication Guides; communication plans; RiskMAPs) for initial drug approvals. Yet, FDA’s regulatory options were more limited to address new safety concerns that arose *after* a drug’s approval.³⁸ Before marketing began, FDA could condition a drug’s approval upon certain indications, warnings, and directions in the product labeling, but after ap-

33. *Id.*

34. U.S. Food & Drug Admin., *Questions and Answers About Lotronex* (June 7, 2002), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110859.htm> (“GSK has agreed to implement a Prescribing Program for Lotronex. Physicians enrolled in the Prescribing Program for Lotronex will agree to inform patients of the risks and benefits of Lotronex and to have patients sign a Patient-Physician Agreement indicating that they understand these risks and benefits. Enrolled physicians will then affix a sticker, which identifies the physician as a participant in the Prescribing Program for Lotronex, to each Lotronex prescription. This sticker will allow the pharmacist to identify that the prescription was written by a physician enrolled in the Prescribing Program for Lotronex.”).

35. Am. Pharmacists Ass’n, *supra* note 31, at 731.

36. *See* U.S. FOOD & DRUG ADMIN., *supra* note 5, at 4–5.

37. INST. OF MED., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* 157 (2007) (“After approval . . . unless a case meets the statutory definition of fraud or misbranding or the high threshold for proving imminent hazard to the health of the public, FDA’s regulatory and enforcement options generally lie at the ends of the spectrum of regulatory actions: do nothing or precipitate the voluntary withdrawal of the drug.”); *see also* U.S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 13, at 10 (“FDA does not have explicit authority to require that drug sponsors take other safety actions; however, when FDA identifies a potential problem, sponsors generally negotiate with FDA to develop a mutually agreeable remedy to avoid other regulatory action.”).

38. U.S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 13, at 10; INST. OF MED., *supra* note 37, at 157 (“FDA relies on firms to withdraw drugs from the market voluntarily when safety issues are revealed.”).

proval, there was no clear statutory authority for FDA to require a drug sponsor to amend the drug's labeling with new safety information.³⁹ As previously explained, FDA also lacked explicit statutory authority after a drug's approval to require the drug sponsor to make specific communications to patients and healthcare providers or place conditions on continuing distribution.⁴⁰ Instead, FDA could only resort to more extreme legal measures, such as withdrawing a drug's approval through administrative procedures or enjoining marketing with a federal enforcement action.⁴¹ These approaches were awkward and less appropriate when FDA believed only intermediate steps were necessary to maintain the appropriate risk-benefit balance for a drug's use, such as stronger warnings on labels. Because of these concerns, FDA typically negotiated additional safety steps directly with the drug sponsor, but this approach could result in a compromise agreement and further delay.⁴²

With highly publicized adverse events and drug withdrawals continuing throughout this period,⁴³ FDA asked the Institute of Medicine (IOM) to assess these problems and revisit FDA's regulatory system for ensuring drug safety.⁴⁴ The IOM issued its findings in

39. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES—IMPLEMENTATION OF SECTION 505(O)(4) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 2 (2011) (“In the past, FDA has requested that holders of applications for approved products make labeling changes related to safety after approval to address serious risks In most cases, application holders responded to these requests for labeling changes by negotiating appropriate language with FDA staff to address the concerns and then submitting a supplement or amended supplement to obtain approval of the changes. Negotiations were often protracted, and FDA had few tools at its disposal to end negotiations and require the changes.”); *see also* INST. OF MED., *supra* note 37, at 157.

40. INST. OF MED., *supra* note 37, at 157; *see also* U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 13, at 10.

41. 21 C.F.R. § 314.200 (2013); *see* 21 U.S.C. §§ 331–332, 334 (2012).

42. INST. OF MED., *supra* note 37, at 157; *see also* U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 13, at 10; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES, *supra* note 39, at 2.

43. *See, e.g.*, Press Release, U.S. Food & Drug Admin., FDA Issues Public Health Advisory on Vioxx as Its Manufacturer Withdraws the Product (Sept. 30, 2004), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108361.htm>; *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES, Nov. 14, 2004, <http://www.nytimes.com/2004/11/14/business/14merck.html>; *see also* U.S. Food & Drug Admin., *Safety: Baycol*, *supra* note 17; *FDA Statement on Baycol Withdrawal*, USA TODAY, Aug. 8, 2001, <http://www.usatoday.com/money/general/2001-08-08-bayer-fda-statement.htm>.

44. INST. OF MED., *supra* note 37, at 21–24 (“[I]n response to growing public concern with health risks posed by prescription drugs, FDA requested that the Institute of Medicine . . . convene an ad hoc committee of experts to conduct an independent assessment of the current system for evaluating and ensuring drug safety and to make

a 2007 report, *The Future of Drug Safety*, which included recommendations for statutory changes to strengthen FDA's drug safety authorities.⁴⁵ As a result of the report, Congress recognized the legal challenges faced by FDA in requiring post-approval safety conditions for prescription drugs and enacted FDAAA in 2007 to address this problem.⁴⁶

A. *FDAAA Authorities for Drug Safety*

FDAAA provided FDA with new regulatory mechanisms to allow the continued marketing of prescription drugs that benefit patients, but with additional conditions that helped decrease adverse event risks.⁴⁷ According to FDAAA, FDA can condition the initial approval or continued marketing of a new drug on compliance with certain stipulations. FDAAA authorizes FDA to require a drug sponsor to conduct post-marketing studies, make labeling changes, and implement Risk Evaluation and Mitigation Strategies (REMS) for a drug.⁴⁸ Importantly, the failure to comply with any of these required conditions is a prohibited act under the statute, which is subject to enforcement action by FDA, including civil or criminal proceedings.⁴⁹ Before FDAAA, the statute did not provide FDA with this authority for post-marketing studies, including labeling changes, and REMS.⁵⁰

FDAAA provides explicit authority for FDA to condition a drug's approval and continued marketing on the development of and adherence to a REMS, which is a plan to ensure the drug's safe use through written communications to patients and/or healthcare providers, as well as restricted distribution conditions for more serious risks.⁵¹ In this way, a REMS can incorporate the RiskMAP approach.⁵² In fact, FDAAA allows FDA to convert pre-FDAAA voluntary RiskMAPs into REMS if certain statutory conditions are satisfied. Thus, when FDAAA became effective on March 25, 2008, FDA con-

recommendations to improve risk assessment, surveillance, and the safe use of drugs.”).

45. *Id.* at 167–76.

46. *See* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2008).

47. 21 U.S.C. §§ 355-1, 355(o)(3), 355(o)(4) (2012).

48. *Id.*

49. 21 U.S.C. §§ 331(d), 332–334, 355(o), 355(p).

50. 21 U.S.C. §§ 301-399.

51. 21 U.S.C. § 355-1.

52. *See supra* notes 29–42 and accompanying text.

verted sixteen RiskMAPs into REMS.⁵³ FDAAA also mandates that a drug shall not be distributed in interstate commerce if its sponsor fails to satisfy any REMS requirements.⁵⁴ A drug's distribution in violation of this provision constitutes a prohibited act under the FDC Act, which is subject to civil actions, such as seizures and injunctions, and criminal proceedings initiated by the United States Department of Justice and FDA.⁵⁵

FDAAA also establishes important parameters for the development and implementation of a REMS. First, the law clarifies that a REMS may be required for the initial approval of a drug or after approval based on new safety information.⁵⁶ The fundamental condition for any REMS to be required is the need to ensure that the drug's benefits outweigh its risks.⁵⁷ FDAAA also clarifies that FDA must consider certain factors in requiring a REMS, such as the size of the population likely to use the drug, disease seriousness, expected benefit, treatment duration, and adverse event seriousness.⁵⁸

The law carefully crafts the relevant definitions for conditions that can trigger a REMS. First, FDAAA broadly defines "new safety information" triggering a REMS for an already-marketed drug as information derived from a clinical trial, an adverse event report, a post-approval study, peer-reviewed medical literature, FDA's post-market risk identification and analysis system, or other scientific data deemed appropriate by the agency.⁵⁹ Second, FDAAA generally requires a REMS to address a drug's "serious risks," which are adverse drug experiences resulting in death, immediate risk of death, inpatient hospitalization, persistent or significant incapacity, or a congenital anomaly or birth defect.⁶⁰

FDAAA establishes three main elements for REMS content. First, FDA can require that a REMS include a Medication Guide for

53. 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, 16,314 (Mar. 27, 2008).

54. 21 U.S.C. § 355(p).

55. 21 U.S.C. §§ 331(d), 332–34.

56. 21 U.S.C. § 355-1(a).

57. *Id.*

58. *Id.*

59. 21 U.S.C. § 355-1(b)(3). This information can pertain to a known serious risk or an unexpected serious risk (*i.e.*, one not included in the drug's labeling), as well as the effectiveness of a current REMS. *Id.*

60. 21 U.S.C. § 355-1(b)(4). To trigger a REMS, the adverse drug experiences must occur in the course of the drug's professional practice use, or result from the drug's abuse, misuse, withdrawal, or failure. 21 U.S.C. § 355-1(b)(1).

patients about a drug's risks.⁶¹ Second, FDA can require that a REMS include a communication plan to health care providers about a drug's risks and the REMS conditions.⁶² Third, FDA can require even stronger elements to assure safe use⁶³—such as restricted distribution—because of a drug's inherent toxicity or potential harmfulness.⁶⁴ These stronger elements must, *inter alia*, be commensurate with the specific serious risk, posted publically by FDA with explanation, and not be unduly burdensome on patient access to the drug.⁶⁵ In conjunction with these elements, FDA can require an “implementation system.”⁶⁶ Such a system may provide for monitoring and evaluating the implementation of elements to assure safe use by health care providers, pharmacists, and other parties.⁶⁷

Under the statutory framework, FDA informs a drug sponsor that a REMS is required and what the necessary components will be.⁶⁸ The drug sponsor then submits a proposed REMS to FDA that addresses these components.⁶⁹ For an initial drug approval, the drug sponsor submits the proposed REMS in the original application to FDA.⁷⁰ For a drug that is already approved and marketed, the drug sponsor submits the proposed REMS in a supplemental application to FDA.⁷¹ FDAAA provides detailed procedures for FDA's review of a proposed REMS, and dispute resolution procedures for any disagreements with the drug sponsor.⁷² Drug sponsors must submit an assessment to FDA eighteen months, three years, and seven years after the REMS was approved, or under an alternative schedule approved by FDA.⁷³ In addition, REMS may be modified or withdrawn by FDA based on new safety or effectiveness information.⁷⁴

61. 21 U.S.C. § 355-1(e)(2).

62. This can be accomplished by sending letters to physicians or disseminating information to professional societies. 21 U.S.C. § 355-1(e)(3).

63. Elements to assure safe use may include health care provider education and training, pharmacy certification, restrictions on use settings, specific patient monitoring, and patient registry enrollment. 21 U.S.C. § 355-1(f)(3).

64. 21 U.S.C. § 355-1(f)(1).

65. 21 U.S.C. § 355-1(f).

66. 21 U.S.C. § 355-1(f)(4).

67. *Id.*

68. 21 U.S.C. § 355-1(a).

69. *Id.*

70. 21 U.S.C. § 355-1(a)(1).

71. 21 U.S.C. § 355-1(a)(2).

72. 21 U.S.C. § 355-1(h). Ultimately, after exhausting these administrative remedies, FDA may issue an order requiring a REMS with the necessary elements. 21 U.S.C. § 355-1(h)(5)(G).

73. 21 U.S.C. § 355-1(d).

74. 21 U.S.C. § 355-1(g). The Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, 126 Stat. 993 (2012), was enacted in July

B. FDA's Implementation of REMS

FDA began implementing the REMS provisions on March 25, 2008, when FDAAA became effective.⁷⁵ FDA has required REMS for new drugs upon initial approval, as well as for products that have already been approved and are on the market.⁷⁶ These REMS have included combinations of three main components: (1) Medication Guides; (2) communications plans; and (3) elements to assure safe use. Some of the REMS with elements to assure safe use also have included implementation systems.⁷⁷

FDA issued draft guidance in September 2009 with recommendations about the content and format of a REMS under the FDAAA provisions.⁷⁸ The draft guidance also recommended that a REMS "supporting document" be submitted to FDA by the drug sponsor in addition to the REMS itself.⁷⁹ Essentially, the supporting document provides the justification for the proposed REMS and the rationale for its various elements. FDA's draft guidance recommended that each supporting document include: (1) background; (2) goals; (3) supporting information about proposed REMS elements; (4) REMS assessment plan; and (5) other relevant information.⁸⁰

2012, reauthorizing FDA's user fee programs and providing additional authorities for drug safety. The law made minor changes to the REMS provisions in the FDC Act, such as for REMS modifications.

75. *Approved Risk Evaluation and Mitigation Strategies (REMS)*, U.S. FOOD & DRUG ADMIN., (2012), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety-InformationforPatientsandProviders/ucm111350.htm>; see also U.S. Food & Drug Admin., 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. 16313 (Mar. 27, 2008).

76. *Approved Risk Evaluation and Mitigation Strategies (REMS)*, *supra* note 75.

77. See, e.g., CTR. FOR DRUG EVALUATION & RESEARCH, RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR LOTRONEX (ALOSETRON HYDROCHLORIDE) TABLETS NDA 21-107 (2010), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM227960.pdf>.

78. U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS), REMS ASSESSMENTS, AND PROPOSED REMS MODIFICATIONS 7-16 (2009), available at <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>. The draft guidance recommended that each proposed REMS include: (1) product and contact information; (2) goals; (3) additional potential REMS elements, such as a Medication Guide and communication plan, if applicable; (4) elements to assure safe use, if applicable; (5) implementation system, if applicable; and (6) timetable for submission of the REMS assessment. *Id.*

79. *Id.* at 7.

80. *Id.* at 16-21. For background, the supporting document should explain the reasons for adopting a REMS and how the proposed REMS would ensure that the benefits of the drug outweigh the risks. For goals and proposed elements, the supporting document should explain the reasons for the proposed goals, how each proposed ele-

FDA issued final guidance in November 2011 addressing distribution requirements for Medication Guides within a REMS.⁸¹ FDA explained in the final guidance that the agency would not enforce the regulatory requirements for Medication Guide distribution in in-patient settings, such as hospitals, where healthcare professionals oversee administration of drugs.⁸² FDA clarified in the final guidance that all Medication Guides must meet the applicable regulatory requirements, but that not every Medication Guide will necessarily be part of a REMS.⁸³

FDA held a public meeting with stakeholders in July 2010 to discuss its implementation of REMS.⁸⁴ The American Pharmacists Association (APhA) also held stakeholder meetings in July 2009⁸⁵ and October 2010⁸⁶ to discuss REMS implementation and issued an APhA white paper with recommendations.⁸⁷ Various other stakeholders, such as healthcare organizations, expressed some concerns with FDA's im-

ment furthers these goals, and how these elements will mitigate the applicable risks. *Id.* at 17–18. The supporting document should also explain the rationale for any proposed REMS assessment. *Id.* at 18–21.

81. U.S. FOOD & DRUG ADMIN., GUIDANCE: MEDICATION GUIDES—DISTRIBUTION REQUIREMENTS AND INCLUSION IN RISK EVALUATION AND MITIGATION STRATEGIES (REMS) 5–9 (2011) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm244570.pdf>.

82. *Id.* at 5–7. FDA also clarified that this enforcement exemption would apply to Medication Guide distribution when healthcare professionals administer drugs in an outpatient setting, such as a clinic or dialysis center. *Id.* But, FDA will enforce the requirements for a Medication Guide's distribution when a drug is dispensed to an outpatient setting for the first time for professional administration to a patient or after a Medication Guide has materially changed. *Id.*

83. *Id.* at 7. The guidance further states that FDA expects to include a Medication Guide within a REMS only when a REMS includes elements to assure safe use. *Id.* at 7–8. This same approach for Medication Guides was described in an earlier FDA draft guidance. See Draft Guidance for Industry on Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies; Availability, 76 Fed. Reg. 10908 (Feb. 28, 2011). After the draft guidance was issued in February 2011, FDA approved two Medication Guide-only REMS before March 24, 2012. In addition, FDA released 93 Medication Guides from approved REMS plans between February 2011 and March 24, 2012.

84. *Risk Evaluation and Mitigation Strategy (REMS) Public Meeting*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/newsevents/ucm210201.htm> (last updated Apr. 17, 2013); see also Kate Traynor, *Stakeholders Urge Overhaul of REMS Programs*, 67 AM. J. HEALTH-SYS. PHARMACY 1397 (2010).

85. The APhA issued a 2009 white paper based on this meeting with recommendations for FDA's implementation of REMS. Am. Pharmacists Ass'n, *supra* note 31.

86. The APhA issued a subsequent 2011 white paper based on this meeting that addressed stakeholder concerns with FDA's implementation of REMS and recommended specific steps. Am. Pharmacists Ass'n, *APhA 2011 REMS White Paper: Summary of the REMS Stakeholder Meeting on Improving Program Design and Implementation*, 51 J. AM. PHARMACISTS ASS'N 340 (2011).

87. *Id.* at 354–355; Am. Pharmacists Ass'n, *supra* note 31, at 741.

plementation of the REMS requirements. In particular, these groups have asked FDA to establish more uniform approaches for REMS.⁸⁸ Healthcare groups whose members are subject to REMS, such as pharmacists who must be certified or trained, have noted that restricted distribution plans under REMS differ in procedures and policies between drugs.⁸⁹ These groups have recommended that FDA establish clear objectives and metrics before each REMS is implemented to assess more accurately the REMS's effect.⁹⁰

The Tufts Center for the Study of Drug Development surveyed various stakeholders in 2011—including payers, pharmacists, health-care providers, patients, and biopharmaceutical companies—about REMS implementation.⁹¹ According to the study's findings, these diverse health care constituencies generally agreed that FDA's REMS program imposed excessive costs and burdens for implementation and was not an improvement over FDA's previous risk management system.⁹² Much of this feedback, though, has been based only on stakeholders' personal experiences with REMS, rather than a rigorous, systematic analysis of the REMS program. In our study we aimed to conduct a more comprehensive review of FDA's REMS implementation, particularly by analyzing the details of each REMS, and identifying important policy implications from this review.

II.

A FOUR-YEAR ANALYSIS OF REMS EMPLOYED BY FDA

To understand how FDA has employed REMS, we collected and analyzed all REMS that have been required in the four-year period since FDAAA's effective date of March 25, 2008.⁹³ Our analysis in-

88. See, e.g., Am. Pharmacists Ass'n *supra* note 86, at 354; see also Philip E. Johnson et al., *NCCN Oncology Risk Evaluation and Mitigation Strategies White Paper: Recommendations for Stakeholders*, 8 J. NAT'L COMPREHENSIVE CANCER NETWORK S7, S17–S19 (2010).

89. See Am. Pharmacists Ass'n, *supra* note 86, at 348–49; see also Johnson et al., *supra* note 88, at S12.

90. These groups have also emphasized the importance of prospectively identifying the specific risks to be mitigated by each REMS, the outcomes to be measured for that REMS, and the strategies for measurement. See Am. Pharmacists Ass'n, *supra* note 31, at 740–42; see also Johnson et al., *supra* note 88, at S20.

91. Tufts Ctr. for Study of Drug Dev., *U.S. Healthcare Stakeholders Uncertain on Benefits of Risk Evaluation Strategy*, 13 TUFTS CSDD IMPACT REP. 1 (2011).

92. It is important to note that the survey sample was small, consisting of 47 respondents. Andrew Wilson & Christopher-Paul Milne, *FDA's Risk Evaluation and Mitigation Strategies (REMS): Effective and Efficient Safety Tools or Process Poltergeist?* 66 FOOD & DRUG L.J. 569, 573 (2011).

93. The time period for this analysis concluded on March 24, 2012, which included four full years in which FDA had the authority to implement REMS.

cludes those REMS that were released (*i.e.*, no longer required) by FDA during this time period. We considered the types of drug indications and diseases that have received a REMS and, when data availability permits, we examined the nature of new safety information, such as the type of studies and adverse event reports related to a particular REMS.

All information about REMS was obtained from publically available documents on FDA's website.⁹⁴ FDA lists each drug with a currently approved REMS in alphabetical order on a dedicated REMS webpage.⁹⁵ This list is updated periodically to incorporate the most recently approved REMS, but there can be a delay between date of approval and date of posting.⁹⁶ Each drug entry on the list has a hyperlink to its approved REMS, which includes the relevant Medication Guide, communication plan, and/or elements to assure safe use as an appendix.⁹⁷

In many cases, an approved REMS does not state a drug's relevant indications or diseases, and several REMS do not state specific safety concerns.⁹⁸ None of the REMS describe the supporting evidence for the safety concerns, such as studies or adverse event reports. For example, many REMS with only Medication Guides and/or communication plans simply state that the REMS is to inform patients and/or healthcare providers about the drug's "serious risks."⁹⁹

94. *Postmarket Drug Safety Information for Patients and Providers*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm> (last updated Mar. 8, 2012).

95. *Approved Risk Evaluation and Mitigation Strategies (REMS)*, *supra* note 75.

96. The search of this website concluded on June 9, 2012. Therefore, any REMS that were approved by March 24, 2012 but posted after June 9, 2012 would not be included in our analysis. For consistency, this article follows the FDA's listings for the purpose of counting REMS. Therefore, one REMS with multiple dosage forms is counted as one REMS, while multiple REMS for the same drug (but with different dosage forms or indications) are counted as multiple REMS.

97. *Approved Risk Evaluation and Mitigation Strategies (REMS)*, *supra* note 75.

98. *See, e.g.*, ANDA 74-703 METOCLOPRAMIDE ORAL SOLUTION RISK EVALUATION AND MITIGATION STRATEGY (REMS) (2009), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187134.pdf> (REMS does not state drug indication); NDA 20-711 ZYBAN (BUPROPION HYDROCHLORIDE) SUSTAINED-RELEASE TABLETS RISK EVALUATION AND MITIGATION STRATEGY (REMS) (2010), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM331982.pdf> (REMS only states for "serious risks").

99. *See, e.g.*, NDA 21-015 ANDROGEL (TESTOSTERONE GEL) 1% CIII RISK EVALUATION AND MITIGATION STRATEGY (REMS) (2011), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM248441.pdf>.

Information about safety concerns and supporting evidence should be provided in the REMS supporting document, described in the 2009 guidance,¹⁰⁰ rather than in the REMS itself. REMS supporting documents, which are submitted to FDA by the drug sponsor, are generally not accessible from FDA's website. Fortunately, other tools on FDA's website can be employed to identify and access additional information about each REMS.¹⁰¹ For example, we consulted the Drugs@FDA website, which contains a searchable database for all approved drugs, to obtain additional information about each REMS.¹⁰² For each newly approved drug, the Drugs@FDA website provides a hyperlink to the FDA approval correspondence and review package, which includes memoranda summarizing the agency's review of the drug's safety and effectiveness evidence, including REMS evaluations.¹⁰³ For drugs already being marketed—for which FDA requires a supplemental application to approve a new REMS—the Drugs@FDA website typically only includes the FDA approval letter for the supplemental application and not the review package.¹⁰⁴ Thus, for most already-marketed drugs, the FDA approval letter is the only other source for additional REMS information available through the FDA website.¹⁰⁵ In these circumstances, one can consult a drug's currently ap-

100. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS), *supra* note 78, at 7–16.

101. Many REMS that were initially required by FDA and implemented by drug sponsors were subsequently released by FDA. These released REMS are not included in the currently approved REMS list on the REMS webpage, but instead are listed separately. *Released Risk Evaluation and Mitigation Strategies (REMS)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm#Releases> (last updated Jan. 7, 2014). The released REMS list does not include hyperlinks to any additional information, such as the REMS itself, FDA correspondence releasing the specific REMS, or the drug sponsor request.

102. *Drugs@FDA*, *supra* note 11. This database includes a separate webpage for each listed drug with hyperlinks to the currently approved drug labeling, REMS, Medication Guide (if applicable), and FDA correspondence approving and releasing (if applicable) the REMS.

103. The review package also includes an agency memorandum describing the REMS justification and supporting evidence. For many of these newly approved drugs, the review package includes correspondence and/or emails about the REMS between FDA officials and the drug sponsor.

104. FDA does not typically post agency review packages for approved supplemental drug applications. U.S. FOOD & DRUG ADMIN., THE FUTURE OF DRUG SAFETY—PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC: FDA'S RESPONSE TO THE INSTITUTE OF MEDICINE'S 2006 REPORT 14 (2007), *available at* <http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm171627.pdf>.

105. For original drug approvals with REMS, FDA's approval letter states the approved indications and relevant diseases. For already-marketed drugs, FDA's supple-

proved labeling, which is hyperlinked for each drug listed on the Drugs@FDA website, and the Medication Guide, if applicable, to understand the safety risks for the drug that might justify a REMS.¹⁰⁶ But, neither the labeling¹⁰⁷ nor the Medication Guide¹⁰⁸ describe or explain the corresponding REMS.

During the first four years of REMS implementation, from March 25, 2008 through March 24, 2012, FDA approved 203 REMS in original and supplemental drug applications.¹⁰⁹ Of these, 108 were released

mental approval letter for the REMS in some cases does not state the approved indications or diseases. *See, e.g.*, Letter from Badrul A. Chowdhury, Ctr. for Drug Evaluation & Research, to Kevin C. Fitzgerald, Director, Regulatory Affairs, GlaxoSmithKline (Mar. 2008), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/021077s041ltr.pdf. In these situations, we consulted the drug's approved labeling, which was accessible via Drugs@FDA. Through this method, relevant information to identify each drug's indication(s) and/or disease(s) was obtained. In some cases, FDA correspondence approving a REMS explains the justification for the safety elements, including a description of new safety concerns and related evidence. *See, e.g.*, Letter from Ozlem Belen, Ctr. for Drug Evaluation & Research, to Robert Dettery, Vice-President, Regulatory Affairs, AR Holding Company, Inc. (June 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/021799s011ltr.pdf. In other cases, FDA approval correspondence does not explain the justification or describe the evidence for the required REMS. For example, the REMS approval letters for some already-marketed drugs do not describe the evidence justifying the REMS but simply reference FDA's initial request letter with the justification. *See, e.g.*, Letter from Ozlem Belen, Ctr. for Drug Evaluation & Research, to Janet Herrington, Deputy Director, Regulatory Affairs, Bayer Pharms. Corp., *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2009/019537s070,019847s044ltr.pdf. These initial FDA request letters for already-marketed drugs are not currently available on the FDA website, with the exception of Avandia and Wellbutrin XR. In addition, the drug sponsor's correspondence responding to FDA's initial request letter is also excluded from the website.

106. For those drugs with REMS that FDA subsequently released, we consulted the Drugs@FDA website to locate the FDA correspondence releasing the REMS. Almost all of these REMS were released between March 25, 2011 and March 24, 2012. We recorded all of the publically available information about these REMS before they were released and removed from FDA's website.

107. A prescription drug's labeling includes comprehensive safety information for health care professionals, but this labeling does not provide information about the corresponding REMS, nor does it state which safety concern triggered the REMS requirement. 21 C.F.R. §§ 201.56, 201.57 (2013).

108. The Medication Guide is an element of the REMS itself and includes all relevant safety information for patients. When a Medication Guide describes multiple safety issues for patients, it may not be possible to determine if one safety concern in particular triggered the REMS requirement. *See, e.g.*, MEDICATION GUIDE: DARVONIN® (C-IV) (PROPOSPHENE NAPSYLATE) (2009), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM187068.pdf>. Also, the Medication Guide typically does not provide details for patients about safety evidence, such as clinical trials or adverse event reports.

109. Sixteen RiskMAPs were incorporated as approved REMS on March 25, 2008. Of these, eleven are included in the 203 REMS total because they were modified since March 2008 and explicitly approved by FDA in supplemental applications. These

by FDA by March 24, 2012.¹¹⁰ We categorized the ninety-five approved REMS and 108 released REMS into four categories—Medication Guide; communication plan; Medication Guide and communication plan; and elements to assure safe use.¹¹¹

Of the ninety-five approved REMS, twenty-four consisted only of Medication Guides and twenty only of communication plans. Nineteen consisted of Medication Guides and communication plans. Finally, thirty-two consisted of elements to assure safe use.¹¹² Of the 108 REMS released by March 24, 2012, ninety-six consisted only of Medication Guides, eleven consisted of both Medication Guides and communication plans, and one consisted of elements to assure safe use.¹¹³ Of the ninety-five approved REMS, forty-nine were for new drug applications and forty-six were for supplemental applications.¹¹⁴ Within the 108 released REMS, thirty-one were for new drug applications and seventy-seven were for supplemental applications.¹¹⁵

eleven REMS are for Actiq, Isotretinoin, Letairis, Lotronex, Mifeprex, Revlimid, Soliris, Thalomid, Tikosyn, Tracleer, and Tysabri. *See Approved Risk Evaluation and Mitigation Strategies (REMS)*, *supra* note 75. The other five incorporated RiskMAPs are not included in the 203 total because FDA's decisions to require specific safety elements were not made under the new FDAAA drug safety framework.

110. In addition, three REMS were folded into two class-wide REMS. A class-wide REMS is a single REMS that applies to multiple drugs. FDA established class-wide REMS for isotretinoin products and transmucosal immediate-release fentanyl products in early 2012. One REMS was subsequently incorporated in the class-wide isotretinoin REMS and two were subsequently incorporated in the class-wide fentanyl REMS.

111. Some of these REMS were originally approved in one category, such as a Medication Guide and communication plan, but were subsequently converted to a different category by the end of the four-year period, such as a communication plan only. The list of ninety-five approved plans is based on the content of each REMS as of March 24, 2012.

112. Of these thirty-two, twenty-eight also included implementation systems. Some of the REMS with elements to assure safe use also included Medication Guides and/or communication plans.

113. None of the released REMS consisted only of communication plans. No REMS with only communication plans were approved before March 25, 2011.

114. For new drug applications, thirty-five out of forty-nine REMS consisted of Medication Guides only, communication plans only, or both Medication Guides and communication plans; the remaining fourteen included elements to assure safe use. For the supplemental applications, twenty-eight out of forty-six REMS consisted of Medication Guides only, communication plans only, or both Medication Guides and communication plans, while the remaining eighteen included elements to assure safe use.

115. For new drug applications, twenty-eight out of thirty-one released REMS consisted of Medication Guides, while three out of thirty-one REMS consisted of both Medication Guides and communication plans. For the supplemental applications, sixty-eight out of seventy-seven REMS consisted of Medication Guides, while eight consisted of both Medication Guides and communication plans. The remaining one out of seventy-seven REMS included elements to assure safe use.

The ninety-five approved REMS cover thirty-three categories of drugs,¹¹⁶ including drugs treating pain; COPD or asthma; Type-2 diabetes; cancer or cancer-related conditions; testosterone-replacement; and cardiovascular or stroke. The 108 released REMS cover twenty-four categories of drugs, including drugs treating seizures and epilepsy; hepatitis-C; HIV-1; osteoporosis, and antibiotics.

The safety concerns¹¹⁷ for the drugs with approved Medication Guide-only REMS range from the risk of congestive heart failure and bladder cancer, to tardive dyskinesia and suicidal thoughts and behavior.¹¹⁸ Based on publically available documents, the evidence base for these REMS generally derives from adverse event reports demonstrating serious risks, although for some drugs the evidence derives from clinical trial information.¹¹⁹ The safety concerns for the drugs with pending communication plan-only REMS include the risk of asthma-related death, anaphylaxis, and acute pancreatitis and medullary thy-

116. We categorized REMS by type of drug, based on the applicable indication or disease treatment. For example, diabetes, antibiotics, and oncology-related drugs are grouped in their own separate categories. Although this categorization does not consider more refined differences in indications between drugs within a category, any such differences should not impact the general conclusions from our analysis. This categorization approach provides a fundamental framework to compare the approved and released REMS.

117. For each drug category, we identified types of safety concerns and related evidence. For some drugs, it was not possible to identify many details about these safety concerns because of limitations in the publically available data.

118. *See, e.g.*, Letter from Mary H. Parks, Ctr. for Drug Evaluation & Research, to Sandra Cosner, Manager, Regulatory Affairs, Takeda Global Research & Development Ctr. (Sept. 14, 2009), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2009/021842s009ltr.pdf (for risk of congestive heart failure); Letter from Amy G. Egan, Office of Drug Evaluation II, to Jessie Y. Lee, Manager, Regulatory Affairs, Takeda Global Research & Development Ctr. (Aug. 4, 2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/021073Orig1s043s044-021842Orig1s014s015-022024Orig1s008s007-021925Orig1s010s011ltr.pdf (for risk of bladder cancer); *see also* CTR. FOR DRUG EVALUATION & RESEARCH, APPROVAL PACKAGE FOR: APPLICATION NUMBER: ANDA 73-680/S-018 (2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/anda/2011/073680Orig1s018.pdf (for risk of tardive dyskinesia); Letter from Bob A. Rappaport, Ctr. for Drug Evaluation & Research, to Lilya I. Donohew, Director, Worldwide Regulatory Affairs, Pfizer (Oct. 19, 2009), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2009/021928s011ltr.pdf (for risk of suicidal thoughts or behavior).

119. *See, e.g.*, Letter from Bob A. Rappaport, Ctr. for Drug Evaluation & Research, to Lilya I. Donohew, Director, Worldwide Regulatory Affairs, Pfizer (Oct. 19, 2009), *supra* note 118 (noting adverse event evidence for risks); Letter from Russell Katz, Ctr. for Drug Evaluation & Research, to Sian Bigora, Vice President, Regulatory Affairs, Questcor Pharmaceuticals (Oct. 15, 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/022432s000ltr.pdf (noting clinical trial evidence for risks).

roid carcinoma.¹²⁰ Based on publically available documents, the evidence base for these REMS includes clinical trials or meta-analyses demonstrating the serious risks.¹²¹ The safety concerns for drugs with both a Medication Guide and communication plan in pending REMS include the risk of asthma-related death, serious infections, and QT prolongation in the heart.¹²² Based on publically available documents, the evidence base for these REMS ranges from adverse event reports to multiple clinical trials demonstrating serious risk.¹²³ Finally, the safety concerns for drugs with elements to assure safe use in pending REMS range from the risk of abuse, misuse, overdose, and addiction to increased mortality and poorer tumor outcomes (for oncology-related drugs).¹²⁴ The evidence base for these REMS includes multiple

120. *See, e.g.*, CTR. FOR DRUG EVALUATION & RESEARCH, NDA 022518 DULERA INHALATION AEROSOL (2011), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM217719.pdf> (for risk of asthma related death); CTR. FOR DRUG EVALUATION & RESEARCH, KALBITOR BLA 125277 (2012), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM261985.pdf> (for risk of anaphylaxis); CTR. FOR DRUG EVALUATION & RESEARCH, NDA 22-341 VICTOZA (LIRAGLUTIDE [RDNA ORIGIN] INJECTION) (2011), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM202063.pdf> (for risk of acute pancreatitis and medullary thyroid carcinoma).

121. *See, e.g.*, Letter from Sally Seymour, Ctr. for Drug Evaluation & Research, to Kevin C. Fitzgerald, Director, Regulatory Affairs, GlaxoSmithKline (Nov. 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/020692s035ltr.pdf (noting clinical trials and meta-analysis for risks).

122. *See, e.g.*, Letter from Sally Seymour, Ctr. for Drug Evaluation & Research, to Renee M. Carroll, Director, Regulatory Affairs, Sunovion Pharmaceuticals (Feb. 2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/021912s012ltr.pdf (for serious infections); *see also* CTR. FOR DRUG EVALUATION & RESEARCH, RISK EVALUATION & MITIGATION STRATEGY (REMS) FOR TASIGNA (NIOLOTINIB) NDA 022068 (2011), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM217737.pdf> (for risk of QT prolongation in heart).

123. *See, e.g.*, Letter from Sally Seymour, Ctr. for Drug Evaluation & Research, to Renee M. Carroll, Director, Regulatory Affairs, Sunovion Pharmaceuticals, *supra* note 122 (noting clinical trials and meta-analysis for risks); Letter from Ozlem Belen, Ctr. for Drug Evaluation & Research, to Robert Dettery, Vice-President, Regulatory Affairs, AR Holding Company, Inc., *supra* note 105 (noting adverse events for risks).

124. *See, e.g.*, Letter from Sharon H. Hertz, Ctr. for Drug Evaluation & Research, to Richard Fanelli, Executive Director, Regulatory Affairs, Purdue Pharma L.P. (June 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/021306s000ltr.pdf (for risk of abuse, misuse, overdose, and addiction); AMGEN, INC., BL 103234 EPOGEN/PROCRT (EPOETIN ALFA): RISK EVALUATION AND MITIGATION STRATEGY (2012), *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM200105.pdf> (for risk of increased mortality and poorer tumor outcomes).

clinical trials and animal toxicology studies demonstrating the serious risk.¹²⁵

The types of risks and evidence differ across drugs within each drug category for approved REMS.¹²⁶ By accounting for these differences, REMS can be tailored for particular drugs. For example, the approved REMS for cancer and cancer-related drugs include a mix of Medication Guides, communication plans, and/or elements to assure safe use.¹²⁷ For the stricter REMS plans (*i.e.*, those involving elements to assure safe use), the safety concerns appear to be more significant—such as increased patient mortality—and based on stronger evidence, including from multiple clinical trials.¹²⁸

125. *See, e.g.*, Letter from Patricia Keegan, Ctr. for Drug Evaluation & Research, to Lisa Shamon-Taylor, Senior Manager, Regulatory Affairs, Amgen, Inc. (Feb. 2010), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/103951s5197ltr.pdf (noting clinical trials for risks); GILEAD SCIENCES, INC., HIGHLIGHTS OF PRESCRIBING INFORMATION: LETAIRIS® TABLETS FOR ORAL USE (2009), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022081s0081bl.pdf (noting animal studies for risk to fetus).

126. It is important to note that in many instances one specific safety concern could have a class effect, which would thus impact multiple drugs. For example, REMS for some COPD drugs (Arcapta Neohaler, Brovana, and Perforomist) were triggered by the same meta-analysis study, which concerned a potential class effect for these drugs and asthma-related death. *See, e.g.*, Letter from Sally Seymour, Ctr. for Drug Evaluation & Research, to Renee M. Carroll, Director, Regulatory Affairs, Sunovion Pharmaceuticals, Inc. (Feb. 2011), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021912s012ltr.pdf (noting the meta-analysis study). Likewise, evidence raising safety concerns about a single active ingredient could also impact multiple drugs with that ingredient. *See, e.g.*, RISK EVALUATION AND MITIGATION STRATEGY (REMS): THE IPLEDGE PROGRAM: SINGLE SHARED SYSTEM FOR ISOTRETINOIN (2010), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234639.pdf> (the same REMS to control for significant fetal risk applies to multiple drugs treating severe acne with the same active ingredient isotretinoin).

127. *See, e.g.*, ASTRAZENECA PHARMACEUTICALS LP, NDA 22-405 CAPRELSA (VANDETANIB): RISK EVALUATION AND MITIGATION STRATEGY (2011), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM253441.pdf> (REMS with Medication Guide, communication plan, and elements to assure safe use, for medullary thyroid cancer); CTR. FOR DRUG EVALUATION & RESEARCH, *supra* note 122 (REMS with Medication Guide and communication plan, for leukemia).

128. This was the case for Aranesp and Epogen/Procrit with the risk analysis from multiple clinical trials, as well as Avandia with a large meta-analysis of the risks. In another example, the thyroid cancer drug Caprelsa, which has a cardiovascular risk (QT prolongation), has a stricter REMS (with elements to assure safe use, Medication Guide, and communication plan) compared to the chronic myeloid leukemia drug Tasigna, which has a similar cardiovascular risk (with only a Medication Guide and communication plan). But in this example, the evidence for the thyroid cancer drug risk and its stricter REMS is based on clinical trial data, while the evidence for the leukemia drug risk is based on adverse event reports. These differences illuminate the

III.

POLICY IMPLICATIONS OF FDA'S REMS IMPLEMENTATION

Our analysis of FDA's implementation of REMS over four years reveals several trends, with important policy implications. First, FDA shifted its REMS policy for Medication Guides after March 2011 and significantly reduced the number of REMS that contain only Medication Guides. As part of this shift, FDA began approving REMS with only communication plans after March 24, 2011. Second, there are limitations in the publically available data related to REMS, which make it challenging to determine the specific justification for a particular REMS requirement or release. These limitations also make it more difficult to understand how FDA reaches REMS decisions and the relationships between these decisions, information critical in assessing FDA's implementation of the REMS authorities and the effectiveness of FDA's REMS policies.

A. FDA's Approach to Medication Guides under FDAAA

During the first three years of REMS implementation, from 2008 to 2011, FDA approved 118 Medication Guide-only REMS, nearly two-thirds of the 184 approved REMS during that time. The most prevalent Medication Guide-only REMS were for drugs that treat a range of diseases, including seizures and epilepsy, hepatitis B and hepatitis C, HIV-1, Type 2 diabetes, osteoporosis, depression, antibiotics, insomnia, testosterone deficiency, and gastroesophageal reflux.¹²⁹ The most common risks noted in Medication Guide-only REMS included suicidality, cardiovascular and cerebrovascular events, tendonitis and tendon rupture, and femoral fracture.¹³⁰ For all of these drugs, FDA determined that it was necessary for patients to receive information directly through Medication Guides about the

importance of fitting REMS to individual drug risks, evidence, and other factors relevant for safe use.

129. U.S. Food & Drug Admin., *supra* note 75.

130. *See, e.g.*, Letter from Ozlem Belen, *supra* note 105 (for risk of tendon ruptures); Letter from Audrey Gassman, Ctr. for Drug Research & Evaluation, to Elinor Chen, Director, Worldwide Regulatory Affairs, Merck Sharpe & Dohme Corp. (Jan. 2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/020560s060,021575s020ltr.pdf (for risk of femoral fracture); Letter from Debra Birnkrant, Ctr. for Drug Evaluation & Research, to Rachael Steiner, Associate Director & Liaison, Global Regulatory Affairs, Schering Corp. (June 2008), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2008/125196s000ltr.pdf (for risk of cerebrovascular events); Letter from Russell Katz, Ctr. for Drug Evaluation & Research, to Paul Kirsch, Director, Regulator Affairs, Cephalon, Inc. (Oct. 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/020646s017ltr.pdf (for risk of suicidal thoughts and behavior).

drugs' risks. This determination meant that FDA believed revised drug labeling for healthcare providers would not be adequate on its own to address these risks and a REMS was necessary.

Prior to FDAAA, FDA relied only on the Medication Guide regulation¹³¹ to support its position that a Medication Guide must be provided directly to patients. The new REMS authorities in FDAAA provided several advantages to FDA relative to Medication Guides. First, the statute explicitly authorizes FDA to require Medication Guides through the REMS mechanisms and to enforce compliance with Medication Guide requirements.¹³² Second, the FDAAA authorities allow FDA to require follow-up assessments for Medication Guides at eighteen months, three years, and seven years after a REMS is approved, or under an alternative schedule approved by FDA.¹³³

These assessments are critical to determine whether Medication Guides are effectively addressing drug safety risks. For example, as part of an assessment, FDA could require a drug sponsor to conduct studies to determine whether patients are receiving Medication Guides upon filling prescriptions. The assessment could then delve even more deeply into whether patients understand the risk descriptions. Some of the approved assessment plans under REMS include patient surveys to examine whether patients are receiving and understanding a Medication Guide.¹³⁴ Even more fundamentally, assessments could determine whether patients appropriately changed behavior—such as following up with their physician about a particular risk—based on reading the Medication Guide.¹³⁵

131. 21 C.F.R. § 208 (2013).

132. 21 U.S.C. §§ 355-1(e)(2), 355(p) (2012).

133. 21 U.S.C. § 355-1(d). The Medication Guide regulation, 21 C.F.R. § 208, does not provide for any assessment requirements, and FDA does not require assessments through its labeling regulations. 21 C.F.R. §§ 201.56–201.57. Assessments required through REMS can be enforced via the FDAAA authorities. 21 U.S.C. §§ 331(d), 332–334, 355(p). The failure to submit an assessment by the due date can subject the drug sponsor to enforcement action. 21 U.S.C. §§ 331(d), 332–334, 355(p).

134. *See, e.g.*, CTR. FOR DRUG EVALUATION & RESEARCH, RISK ASSESSMENT AND RISK MITIGATION REVIEW(S): ANDROGEL 1.62% (TESTOSTERONE GEL) (2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022309Orig1s000RiskR.pdf.

135. In a recent Issue Paper, FDA acknowledged the “need to assess health care provider/patient behavior” as part of these REMS assessments. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., RISK EVALUATION AND MITIGATION STRATEGY ASSESSMENTS: SOCIAL SCIENCE METHODOLOGIES TO ASSESS GOALS RELATED TO KNOWLEDGE 1 (2012), *available at* <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM301966.pdf>. Of note, the Medication Guide within a REMS can be amended based on the results of an assessment. 21 U.S.C. § 355-1(g).

1. FDA's Shift in Policy for Medication Guides

FDA changed its approach to Medication Guides with its draft guidance in February 2011,¹³⁶ which it finalized in November 2011.¹³⁷ The guidance clarifies that, in most cases, FDA expects to include Medication Guides in a REMS only when the REMS also includes elements to assure safe use.¹³⁸ FDA can also now require a Medication Guide in the absence of a REMS. Prior to the 2011 guidance, all new Medication Guides since the implementation of FDAAA, in March 2008, were required under a REMS.¹³⁹ The 2011 guidance also described how drug sponsors could submit a supplemental application to request the removal of a Medication Guide from a REMS.¹⁴⁰ The guidance states that any proposed REMS modification must be accompanied by a REMS assessment. This can be a prior REMS assessment that occurred within the previous eighteen months, or an update on the status of a required post-approval study or clinical trial.

The guidance does not provide an explanation for FDA's change in policy for Medication Guides. Specifically, FDA does not clarify why the agency decided that a REMS will no longer be necessary for the issuance of most Medication Guides. The guidance merely states that a Medication Guide-only REMS will be required if the Medication Guide, issued on its own, "will not be sufficient to ensure that the benefits of the drug outweigh the risks."¹⁴¹ FDA does not explain why the additional FDAAA authorities—*e.g.*, requiring periodic assessments of the Medication Guide and enforcing the Medication Guide provisions—would not, in most cases, be necessary to ensure that a drug's benefits outweigh the risks.

Our analysis of extant REMS demonstrates FDA's change in policy. In the first three years of REMS implementation, before the 2011 guidance, FDA approved 118 Medication Guide-only REMS.¹⁴² Many drug sponsors subsequently used the procedures described in the 2011

136. Draft Guidance for Industry on Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies, 76 Fed. Reg. 10,908 (Feb. 28, 2011).

137. U.S. FOOD & DRUG ADMIN., *supra* note 78, at 5–9.

138. *Id.* at 7–8.

139. *Id.* at 4.

140. *Id.* The guidance does not state why a drug sponsor might want to remove a Medication Guide from a REMS. But once a Medication Guide is removed, the drug sponsor would no longer be legally required to submit assessments for the Medication Guide and would not be subject to the FDAAA enforcement authorities.

141. *Id.* at 7–8.

142. *See supra* Part II.B.

guidance to request the removal of Medication Guide-only REMS.¹⁴³ By early 2012, FDA had released ninety-six of the Medication Guide-only REMS and had removed Medication Guides from thirteen REMS that also included communication plans.¹⁴⁴ Finally, FDA approved just two Medication Guide-only REMS from 2011 to 2012. Of note, numerous new or amended Medication Guides were approved during this period without a REMS.¹⁴⁵

FDA's correspondence approving supplemental drug applications that released Medication Guides from REMS is typically posted on the agency's website.¹⁴⁶ In most of these letters, though, FDA simply states that based on findings from the drug sponsor's assessment, the REMS is no longer necessary for the benefits of the drug to outweigh its risks.¹⁴⁷ The correspondence does not explain how FDA made this determination. In general, neither the drug sponsor's REMS assessment nor FDA's internal evaluation are publically available on the agency's website. Thus, it is not possible to identify the specific reasons for FDA's release of a particular REMS.

FDA's correspondence approving new or amended Medication Guides as part of a drug's labeling, but without a REMS, is also posted on the agency's website.¹⁴⁸ For the numerous new or amended Medication Guides that were approved from 2011 to 2012 without a REMS, this publically available information does not explain why a REMS is not necessary for the particular Medication Guide to ensure that the drug's benefits outweigh its risks.¹⁴⁹ Thus, it is not possible to understand the specific reasons that FDA required a Medication Guide without a REMS for each drug.

143. In fact, some have indicated that FDA contacted certain drug manufacturers to request that they submit supplemental applications seeking the release of Medication Guides from REMS. Kate Traynor, *Medication Guides Leave Their REMS Programs Behind*, 69 AM. J. HEALTH SYS. PHARMACY 272 (2012).

144. Between 2011 and 2012, FDA also approved five REMS with only communication plans. FDA had not approved communication plan-only REMS during the first three years of REMS implementation.

145. *Medication Guides*, U.S. FOOD & DRUG ADMIN., (2012), <http://www.fda.gov/drugs/drugsafety/ucm085729.htm>.

146. *Drugs@FDA*, *supra* note 11.

147. *See, e.g.*, Letter from Audrey Gassman, Ctr. for Drug Evaluation & Research, to Matthew Lamb, Senior Director Regulatory Affairs, Warner Chilcott, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020835s044ltr.pdf.

148. *Drugs@FDA*, *supra* note 11.

149. *See, e.g.*, CTR. FOR DRUG EVALUATION & RESEARCH, SUMMARY REVIEW OF REGULATORY ACTION (Mar. 2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125370Orig1s000SumR.pdf. This review includes a Medication Guide. In addressing why a REMS was not necessary for the Medication Guide, the review document simply quotes the new policy from the Medication Guide Draft Guidance without any details specific to the drug in question.

2. Revisiting Drug Sponsors' Assessment Methods for REMS

FDA has continued its efforts to determine the most scientifically valid approaches for assessing the effectiveness of REMS to communicate drug risks to patients and health care professionals.¹⁵⁰ FDA held a public workshop in June 2012 to discuss methods for assessing communications to patients and health care providers required under REMS.¹⁵¹ In particular, FDA was interested in learning more about survey methodologies and related instruments that could be helpful in evaluating patients' and health care providers' knowledge about drug risks under a REMS.¹⁵² For Medication Guides within REMS, it is critical to know whether patients receive the relevant information and, if so, whether they understand this information and change their behavior in appropriate ways.

FDA published a white paper for the public workshop that summarized issues related to assessments of REMS with communication requirements, such as Medication Guides for patients and communication plans for health care providers.¹⁵³ From March 25, 2008 through December 31, 2011, FDA received and reviewed 144 REMS assessments from drug sponsors, including fifty-five for Medication Guide-only REMS and thirty-three for Medication Guide and communication plan REMS.¹⁵⁴ According to the white paper, only cross-sectional surveys¹⁵⁵ have been used to evaluate patients' and health care providers' understanding of a drug's risks and safe use.¹⁵⁶ Importantly, for

150. *Risk Evaluation and Mitigation Strategy (REMS) Assessments: Social Science Methodologies to Assess Goals Related to Knowledge: Public Workshop*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/NewsEvents/ucm292337.htm> (last updated July 9, 2012).

151. *Id.*

152. *Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge: Public Workshop; Issue Paper*, 77 Fed. Reg. 26,292 (May 3, 2012).

153. CTR. FOR DRUG EVALUATION & RESEARCH, *supra* note 135.

154. *Id.* at 2.

155. In a cross-sectional study, investigators assess an outcome in a group of individuals at a single point in time, as opposed to a longer period of time. *See* LEON GORDIS, EPIDEMIOLOGY 195–198 (4th ed. 2009).

156. CTR. FOR DRUG EVALUATION & RESEARCH, *supra* note 135, at 2. For these REMS communication evaluations, drug sponsors surveyed physicians and patients to measure their understanding of a drug's risks and safe use at a single point in time. But, the drug sponsors did not evaluate physician and patient understanding over a period of time, particularly by comparing each group's knowledge before and after the communication plans were implemented.

The white paper explains the limitations of REMS assessments—particularly in their research methodologies—and describes issues that must be addressed to improve the usefulness of cross-sectional surveys in assessing whether REMS are improving patient and health care provider understanding of a drug's risks and safe use. *Id.* at

those Medication Guides that are not required under a REMS or that are released from a REMS, FDA cannot require assessments under its FDAAA authorities. FDA's Medication Guide regulation does not authorize FDA to require these assessments.¹⁵⁷ Thus, FDA's shift away from Medication Guide REMS, with their mandatory assessments, makes it very difficult for the agency to evaluate each Medication Guide's utility and effectiveness. This difficulty appears more pronounced given FDA's acknowledgement of the weaknesses in survey assessment methods and the agency's ongoing efforts to develop valid assessment methods.¹⁵⁸

B. Limitations in the Publicly Available Data

Limitations in FDA's publicly available data impact third parties' ability to analyze the agency's REMS implementation and determine if REMS are helping ensure safer drug use.¹⁵⁹ Drug safety depends on vigilance and communication from individuals outside FDA, such as health care participants and researchers, to the agency. For many drugs, adverse event reporting from health care systems or research from academic organizations has informed FDA of new safety risks and prompted regulatory actions for those drugs.¹⁶⁰ These

3–6. Importantly, the white paper notes that methods other than surveys are available to assess the effectiveness of REMS educational components. *Id.* at 2.

157. 21 C.F.R. §§ 208.1–208.26 (2013).

158. The Office of Inspector General (OIG) for the Department of Health and Human Services confirmed these weaknesses in FDA's REMS program implementation in a 2013 report. OFFICE OF INSPECTOR GENERAL, U.S. DEPT. OF HEALTH AND HUMAN SERVICES, *FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY* (2013). According to the OIG investigation, FDA had determined that many REMS plans were not meeting their specified goals. *Id.* at 16–18. OIG also noted that FDA had not yet developed valid methods to determine the effectiveness of REMS plans in ensuring drug safety. *Id.* at 18–19.

159. *See supra* Part II.A.

160. FDA's Adverse Event Reporting System (FAERS) depends on mandatory report submissions from drug sponsors, as well as voluntary reporting from patients, health care professionals, hospitals, and other outside sources. *FDA Adverse Event Reporting System (FAERS) (formerly AERS)* (2012), U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>. According to the IOM report, FDA receives over 400,000 spontaneous reports every year through FAERS. INST. OF MED., *supra* note 37, at 53. These reports can shape FDA's drug safety decisions. For example, the manufacturer of Baycol, a cholesterol-lowering drug, voluntarily withdrew the drug from the market based on adverse event reports of rhabdomyolysis (significant muscle weakness). Syed Rizwanuddin Ahmad, *Adverse Drug Event Monitoring at the Food and Drug Administration*, 18 J. GEN. INTERN MED. 57, 59 (2003).

Academic research can also influence FDA's drug safety decisions. For example, researchers from outside FDA conducted a meta-analysis from publicly available

principles also apply for those individuals outside FDA who follow and analyze REMS for prescription drugs. Their findings could assist the agency in assessing the effectiveness of individual REMS or overall REMS policies.¹⁶¹ The availability of more REMS information on FDA's website would assist these efforts.

For many drugs there is insufficient information on FDA's website to assess thoroughly the specific drug risks and supporting evidence justifying the REMS.¹⁶² FDA's approval letters for some REMS are not publically available or lack information about the risks that triggered the REMS.¹⁶³ In addition, for almost all already-marketed drugs with subsequently approved REMS, the REMS supporting documents are not accessible via FDA's website.¹⁶⁴ These documents, which are posted in the review packages for newly approved drugs, usually include a thorough analysis of the supporting evidence and REMS justification.¹⁶⁵ Thus, for almost all already-marketed drugs, it

clinical trial data for Avandia (a type 2 diabetes drug) that demonstrated an increased risk for ischemic cardiac events. The results of this analysis led to stronger FDA-mandated label warnings. Steven E. Niesen, *The Rise and Fall of Rosiglitazone*, 31 EUR. HEART J. 773, 774–75 (2010).

161. Some researchers have noted that REMS are “intended to provide data to inform future decisions about the safety of the product, which presumes public disclosure and discussion within the scientific community of monitoring results.” Elizabeth B. Andrews, James A. Kaye, & Carla Van Bennekom, *The REMS Publication Paradox*, 23 ONCOLOGY 715, 715 (2009). The researchers also explained that safety data for certain drugs could be relevant for other drugs in that class, and patient compliance from one REMS program could be relevant for other REMS programs. *Id.* at 721.

162. *See supra* Part II.A.

163. As of August 8, 2012, for those REMS that were still pending, the REMS approval letters for Actos, Wellbutrin XL, and Xeomin were not accessible on FDA's website. In addition, the REMS approval letters for Darvon and Mifeprex do not provide a REMS justification. Letter from Sharon Hertz, Ctr. for Drug Evaluation & Research, to Arthur C. Ilse, Director, Regulatory Affairs, Xanodyne Pharmaceutical, Inc. (Sept. 2009), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/010997s051,052,016862s041,042,017122s061,062ltr.pdf; U.S. Food & Drug Admin., *Supplement Approval NDA 020687/S-014* (2011), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020687s014ltr.pdf.

164. As of August 8, 2012, for already-marketed drugs with new REMS, the FDA REMS review memoranda were only posted for Advair Diskus and Avandia. CTR. FOR DRUG EVALUATION & RESEARCH, SUMMARY REVIEW OF REGULATORY ACTION (2008), available at http://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2008/021077se2-029_SUMR.pdf; CTR. FOR DRUG EVALUATION & RESEARCH, DECISION ON CONTINUED MARKETING OF ROSIGLITAZONE (AVANDIA, AVANDAMET, AVANDARYL) (2010), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM226959.pdf>. In addition, for all already-marketed drugs except for Avandia, FDA's initial letters requiring these REMS and the drug sponsor's response are not publically available on FDA's website.

165. *See supra* Part II.B.

is not possible to ascertain more fully the FDA's REMS analysis and justification through publically available information.¹⁶⁶ Finally, for any given REMS, the follow-up assessments conducted by the drug sponsor and FDA's review of these assessments are not publically available.¹⁶⁷ These limitations in the publically available data pose challenges for individuals interested in better understanding REMS.

1. *FDA's Position for Limiting Publically Available REMS Information*

In its 2007 report, *The Future of Drug Safety*, the IOM recommended that FDA make its review memoranda for supplemental drug applications available through its website.¹⁶⁸ The IOM argued that this would allow the public to more readily understand FDA's assessment of a drug's risks and the relevant evidence base.¹⁶⁹ FDA, however, rejected this approach in its written response to the IOM report.¹⁷⁰ FDA explained that it has publically posted review memoranda for newly approved drug applications since 1998, but that it does not post review memoranda for supplemental applications until requests are submitted under the Freedom of Information Act (FOIA).¹⁷¹ FDA justified this approach based on resource constraints and its view that a dearth of FOIA requests indicated a lack of "informational value" in supplemental application review documents.¹⁷² Of note, FDA provided this response to the IOM before its FDAAA authorities were in place.

166. Even for those already-marketed drugs with new REMS where an FDA approval letter does describe the risks and evidence justifying the REMS, the FDA review memoranda and drug sponsor written assessments are helpful in further explaining the REMS. The review memoranda generally explain FDA's risk analysis and the supporting evidence in much greater detail than the REMS and approval letter. See, e.g., CTR. FOR DRUG EVALUATION & RESEARCH, DECISION ON CONTINUED MARKETING OF ROSIGLITAZONE, *supra* note 164; Letter from Mary H. Parks, Ctr. for Drug Evaluation & Research, to Margaret M. Kreider, Senior Director for Regulatory Affairs, SmithKline Beecham LTD (May 15, 2011), available at http://www.access-data.fda.gov/drugsatfda_docs/appletter/2011/021071s039,021410s027,021700s011ltr.pdf.

167. For those REMS components that were released, the drug sponsor's request letter and FDA's review memoranda are not available on FDA's website. In addition, many of the FDA letters approving a REMS release are not posted on FDA's website. As of August 8, 2012, the REMS release letters were not posted for Cimzia, Enbrel, Extavia, Factive, Infergen, Intron A, Kaletra, Levaquin, and Oleptro. *Drugs@FDA*, *supra* note 11.

168. INST. OF MED., *supra* note 37, at 145–46.

169. *Id.*

170. U.S. FOOD & DRUG ADMIN., *supra* note 104, at 14.

171. *Id.*; Freedom of Information Act, 5 U.S.C. § 552 (2012).

172. U.S. FOOD & DRUG ADMIN., *supra* note 104, at 14.

Although individuals can request information through FOIA requests, FDA can take over a year to provide the information, which would delay any posting of REMS-related documents on the agency's website.¹⁷³ In addition, despite FDA's assertions that FOIA requests are easy to submit, individuals could be subject to fees for these requests.¹⁷⁴ Inefficiencies can also result from different individuals submitting multiple FOIA requests for documents before they are posted. The routine posting of REMS materials on FDA's website would provide the easiest access for the public. Importantly, review packages for supplemental drug applications with approved REMS would constitute only a small subset of all approved supplemental drug applications.¹⁷⁵ Thus, redacting and posting the review memoranda and REMS correspondence between FDA and the drug sponsor, for both the addition and release of a REMS, should not require significant costs.

The drug sponsor's assessment of a REMS is another critical component in determining whether the REMS is enhancing a drug's safe use and limiting its risks. Typically, neither the drug sponsor's REMS assessment nor FDA's evaluation of the assessment are publicly posted. It is unclear if FDA would provide documents related to a REMS assessment in response to a FOIA request.¹⁷⁶ Access to these

173. According to FDA's 2011 FOIA report, a complex FOIA request takes an average of 248 days for FDA to provide documents, with nearly a third of all complex requests taking over 400 days for FDA documents and the longest period taking 1,760 days. A complex FOIA request is placed in a "slower track based on the high volume and/or complexity of the records requested." U.S. FOOD & DRUG ADMIN., FREEDOM OF INFO. ANNUAL REP. 2011 (2011), available at <http://www.fda.gov/Regulatory-Information/FOI/FOIAAnnualReports/ucm295118.htm>. FDA's response to the IOM report suggests that the agency handles FOIA requests for supplemental application documents as complex requests.

174. The fees are required under FOIA, unless waived by the government. 5 U.S.C. § 552. The requester may be entitled to a fee waiver under the FDA FOIA regulations. 21 C.F.R. § 20.46 (2013). See also U.S. Food & Drug Admin., *Frequently Asked Questions (FAQ) for Freedom of Information Topics*, <http://www.fda.gov/Regulatory-Information/FOI/ucm165600.htm#Q9> (last updated Mar. 18, 2011).

175. FDA approves hundreds of supplemental drug applications each year. For example, FDA approved 111 supplemental applications for drug efficacy in 2011, which is just one type of supplemental application for drugs. U.S. FOOD & DRUG ADMIN., NEW DRUG APPLICATION (NDA) & BIOLOGIC LICENSE APPLICATION (BLA) EFFICACY SUPPLEMENT CALENDAR YEAR APPROVALS (2011), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM278501.pdf>.

176. Some researchers assessing REMS have not published their findings because of concerns that the information is prohibited from disclosure by government ethics rules. The Office for Human Research Protection in the U.S. Department of Health and Human Services has informed certain investigators that information from mandatory monitoring programs could not be published in peer-reviewed literature because the activities were not considered research. Institutional Review Boards may

assessments would assist in understanding a REMS's effectiveness and, when applicable, FDA's decision to release a REMS.¹⁷⁷ The public availability of these assessments could also assist social scientists and other experts in providing advice requested by FDA for developing validated assessment methods for REMS.¹⁷⁸

Posting additional REMS information seems more consistent with FDA's recent emphasis on regulatory transparency. In accordance with President Barack Obama's policy directive for more public openness in government,¹⁷⁹ FDA launched a Transparency Initiative in June 2009.¹⁸⁰ The agency created a task force to draft a report with findings and recommendations regarding transparency issues for the FDA Commissioner. The task force held two public meetings and opened a docket for public comments on transparency issues.¹⁸¹ The task force then issued draft proposals for public comment regarding FDA's disclosure policies.¹⁸² Many of these proposals involved recommendations that FDA post more information on its website.¹⁸³ The task force next considered public comments on its proposals as well as feasibility concerns.¹⁸⁴ The task force has not yet issued final proposals. In the meantime, FDA has implemented some of the task force's

refuse to evaluate such mandatory drug safety programs as research. Andrews et al., *supra* note 161.

177. OIG reviewed FDA's evaluation of drug sponsors' assessments for fifty five REMS. See OIG, FDA LACKS COMPREHENSIVE DATA (2013), *supra* note 158 at 10. Although OIG was able to obtain access to FDA and sponsor documents for the REMS assessments, these FDA evaluations and assessment documents are not publicly available on FDA's website. *Id.*

178. See *supra* Part III.A.2.

179. Memorandum from President Barack Obama to the Heads of Executive Dep'ts and Agencies (Jan. 2009), available at http://www.whitehouse.gov/the_press_office/TransparencyandOpenGovernment ("We will work together to ensure the public trust and establish a system of transparency, public participation, and collaboration. Openness will strengthen our democracy and promote efficiency and effectiveness in Government.").

180. FDA Transparency Initiative, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm> (Feb. 1, 2012).

181. U.S. FOOD & DRUG ADMIN., FDA TRANSPARENCY INITIATIVE: DRAFT PROPOSALS FOR PUBLIC COMMENT REGARDING DISCLOSURE POLICIES OF THE U.S. FOOD AND DRUG ADMINISTRATION 2 (2010).

182. *Id.* at 4–8.

183. *Id.* at 4–6. The task force recommended, *inter alia*, that FDA provide public access to certain drug safety information, such as updated adverse event reports and information about significant safety concerns with unapproved new drug applications. *Id.*

184. *Id.* at 63.

draft proposals, but not those related to posting certain drug safety information.¹⁸⁵

Greater transparency will be critical for evaluating individual REMS and the success of FDA's REMS implementation. The REMS approval and assessment information could be used by researchers in various fields to study the utility and effectiveness of individual REMS. For example, when a REMS assessment involves surveillance of a drug's prescribing patterns, epidemiologists could analyze the collected data to determine how the REMS is affecting the prescription drug's use.¹⁸⁶ Where a REMS assessment involves drug knowledge surveys for healthcare providers and patients, social scientists could analyze the survey methodologies and data to determine the validity of the methods and meaningfulness of the results.¹⁸⁷ In addition, the REMS information could also be used for broader policy analysis. For public health researchers assessing FDA's approaches in implementing REMS, as done in this article, additional information about individual REMS would shed more light on the agency's policy decisions in this area.

2. FDA's Approach to Sharing REMS Information for Avandia

FDA's treatment of REMS information for Avandia provides a useful example of the agency engaging in greater transparency about its decision making processes. FDA used its new FDAAA authorities in fall 2010 to restrict the prescribing and dispensing of Avandia, a drug for Type-2 diabetes, based on data suggesting increased cardio-

185. As of January 4, 2014, FDA has not begun implementation for most of these draft proposals. See, e.g., *Phase II Progress Report: FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration*, U.S. FOOD & DRUG ADMIN., (2010), <http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm273854.htm>

186. The REMS approval for Avandia in May 2011 provides such an example, where the assessment plan includes obtaining patient and prescription numbers for the drug's use. Letter from Mary H. Parks, *supra* note 166.

187. Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess goals Related to Knowledge; Public Workshop; Issue Paper, 77 Fed. Reg. 26,292, 26,292 (May 3, 2012) ("The workshop objectives are as follows: (1) Initiate constructive dialogue and information-sharing about survey methodologies and instruments used to evaluate patients' and healthcare providers' knowledge about drugs' risks; (2) share current FDA experience regarding social science assessments of surveys as a component of REMS Assessment Plans; (3) obtain information that will be used to develop standardized survey methodologies for evaluating patient and health care provider knowledge under a REMS; (4) discuss alternative methodologies to surveys to assess knowledge; and (5) discuss the use of surveys as a tool to assess patient and prescriber behavior changes, burden on the health care system, and patient access to the drug under a REMS.").

vascular risk.¹⁸⁸ Specifically, FDA required GlaxoSmithKline (GSK), the drug sponsor, to (1) strengthen the drug's warning label; (2) arrange for independent re-adjudication of critical study results; and (3) implement a REMS with elements to assure safe use that include a restricted distribution program.¹⁸⁹ FDA's decision allowed Avandia use to continue among existing patients who consulted with their doctor about the drug's safety risks and among new patients without viable treatment alternatives. Rather than prohibit marketing altogether in the face of new safety risks, FDA chose to add further conditions to Avandia's distribution.

Because of the significant public attention this matter received,¹⁹⁰ particularly given the millions of patients with diabetes, FDA publically posted its letter to GSK requiring a REMS in September 2010.¹⁹¹ In addition, FDA publically posted the final memorandum justifying its Avandia decision based on scientific and regulatory analysis, as well as supporting documents from FDA staff, including some that recommended alternative approaches.¹⁹² These documents show that the scientific basis for the Avandia decision was grounded in FDA's evaluation of safety data from clinical trials, meta-analysis of multiple trials, and epidemiologic studies comparing Avandia to other diabetes drugs and placebo.¹⁹³ In these publically available documents, FDA carefully explained the strengths and weaknesses of each study and

188. *FDA Significantly Restricts Access to the Diabetes Drug Avandia*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm> (last updated Nov. 25, 2013).

189. Letter from Janet Woodcock, Director, Ctr. for Drug Evaluation & Research, to NDA 021071 (Sept. 22, 2010), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM226959.pdf>. Prior to 2010, FDA had taken incremental steps to strengthen warnings related to Avandia and had required additional risk information to be provided to patients. . *FDA Drug Safety Communication: Ongoing Review of Avandia (Rosiglitazone) and Cardiovascular Safety*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm201418.htm> (last updated Apr. 1, 2010).

190. E.g., Massimo Calabresi, *After Avandia: Does the FDA Have a Drug Problem?* TIME, Aug. 12, 2010, available at <http://www.time.com/time/magazine/article/0,9171,2010181,00.html>; Gardiner Harris, *Diabetes Drug Maker Hid Test Data, Files Indicate*, N.Y. TIMES, July 13, 2010, available at http://www.nytimes.com/2010/07/13/health/policy/13avandia.html?_r=1&ref=avandiadrug; Alicia Mundy & Jennifer Corbett, *Two New Studies Cite Heart Risk in Glaxo's Avandia*, WALL ST. J., June 29, 2010, available at <http://online.wsj.com/article/SB10001424052748703964104575334570859778764.html>.

191. *FDA Significantly Restricts Access to the Diabetes Drug Avandia*, *supra* note 188.

192. *Id.*

193. Letter from Janet Woodcock, *supra* note 189.

the remaining uncertainty over Avandia's safety.¹⁹⁴ FDA approved the Avandia REMS, which was submitted by GSK, on May 18, 2011.¹⁹⁵

While the Avandia example provides a model of transparency, for many prescription drugs FDA's publically available documents do not fully explain the agency's rationale for requiring, or releasing, a REMS. Without this information, stakeholders in the drug policy and regulatory affairs communities cannot fully assess how FDA is implementing REMS under its FDAAA authorities. This limitation may become increasingly important as researchers outside of FDA attempt to evaluate the impact of FDA's REMS implementation on drug safety.

CONCLUSION

FDAAA provided FDA with significant new authorities for regulating prescription drug safety.¹⁹⁶ REMS are an important component of this regulatory framework for assuring the safety and effectiveness of prescription drugs. Our analysis shows that FDA has quickly implemented the REMS provisions since they became effective in March 2008. FDA has required detailed REMS for hundreds of prescription drugs. The breadth of these drug types, risks, and evidence shows the wide scope of the agency's REMS implementation. For example, most of the REMS were required for drugs already on the market,¹⁹⁷ which demonstrates FDA's vigilance in recognizing post-market safety signals.

This article has identified important policy concerns related to FDA's REMS implementation. First, FDA changed its approach to Medication Guides in 2011, by no longer requiring their issuance within a REMS. The agency's justification for this policy shift remains unclear. Of the approximately 200 REMS that were required by

194. *Id.* at 2 ("The evidence pointing to a cardiovascular ischemic risk with rosiglitazone is not robust or consistent. . . . Nevertheless, there are multiple signals of concern, from varied sources of data, without reliable evidence that refutes them. Additionally, evidence available to date, including a randomized trial in high-risk individuals, does not reveal a signal of cardiovascular ischemic risk with the other thiazolidinedione (TZD)-class drug available on the US market, pioglitazone. Therefore, based on this safety information, it is necessary to restrict access to rosiglitazone until more substantial evidence of its safety becomes available.").

195. Letter from Mary H. Parks, *supra* note 166. FDA subsequently announced in November 2013 that some of these REMS and labeling restrictions would be removed based on the agency's evaluation of updated scientific data and advisory committee recommendations. See *FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines*, U.S. FOOD & DRUG ADMIN., (2013), <http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm>.

196. See *supra* Part I.A.

197. See *supra* Part II.A.

FDA since 2008, over half were released between 2011 and 2012. This timing seems odd, given FDA's on-going efforts to develop better methodologies to assess the effectiveness of REMS, and particularly Medication Guides.

Second, much information about FDA's decision to require or release a REMS is not currently publically available. This observation does not imply that health care providers and patients are insufficiently informed about drug safety and effectiveness information. Also, we are not suggesting that FDA has inappropriately required REMS or that drug sponsors have failed to implement them. Rather, this article has demonstrated that there is currently a dearth of publically available information regarding the scientific justification for some REMS and the assessment and release of most REMS, though individual FOIA requests remain a relatively unexplored option. Without access to REMS assessments and FDA's release documents, the public cannot confirm that drug sponsors are correctly implementing REMS, nor can they understand whether REMS are effective.

FDA's transparency initiative appears to support the public availability of this additional REMS information, including FDA's application of the new Medication Guide approach to individual REMS and the agency's requirement, assessment, and release of numerous REMS. This information could be used by researchers in various fields to assess FDA's policies for implementing REMS and whether the scientific evidence supports the requirement, assessment, and, if applicable, release of each REMS. This research, in turn, would help evaluate whether FDA is successfully implementing the REMS program. The goal of these various research efforts is to ensure that REMS are successful in improving drug safety, which is the ultimate goal of the REMS authorities.