

## **EVIDENCE AND EXTRAPOLATION: MECHANISMS FOR REGULATING OFF-LABEL USES OF DRUGS AND DEVICES**

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### ABSTRACT

*A recurring, foundational issue for evidence-based regulation is deciding whether to extend governmental approval from an existing use with sufficient current evidence of safety and efficacy to a novel use for which such evidence is currently lacking. This “extrapolation” issue arises in the medicines context when an approved drug or device that is already being marketed is being considered (1) for new conditions (such as off-label diagnostic categories), (2) for new patients (such as new subpopulations), (3) for new dosages or durations, or (4) as the basis for approving a related drug or device (such as a generic or biosimilar drug). Although the logic of preapproval testing and the precautionary principle—first, do no harm—would counsel in favor of prohibiting extrapolation approvals until after traditional safety and efficacy evidence exists, such delays would unreasonably sacrifice beneficial uses. The harm of accessing unsafe products must be balanced against the harm of restricting access to effective products. In fact, the Food and Drug Administration’s (FDA’s) current regulations in many ways reject the precautionary principle because they largely permit individual*

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*physicians to prescribe medications for off-label uses before any testing tailored to those uses has been done. The FDA's approach empowers physicians, but overshoots the mark by allowing enduring use of drugs and devices with insubstantial support of safety and efficacy. This Article instead proposes a more dynamic and evolving evidence-based regime that charts a course between the Scylla and Charybdis of the overly conservative precautionary principle on one hand, and the overly liberal FDA regime on the other.*

*Our approach calls for improvements in reporting, testing, and enforcement regulations to provide a more layered and nuanced system of regulatory incentives. First, we propose a more thoroughgoing reporting of off-label use (via the disclosure of diagnostic codes and "detailing" data) in manufacturers' annual reports to the FDA, in the adverse event reports to the FDA, in Medicare/Medicaid reimbursement requests, and, for a subset of FDA-designated drugs, in prescriptions themselves. Second, we would substantially expand the agency's utilization of postmarket testing, and we provide a novel framework for evaluating the need for postmarket testing. Finally, our approach calls for a tiered labeling system that would allow regulators and courts to draw finer reimbursement and liability distinctions among various drug uses, and would provide the agency both the regulatory teeth and the flexibility it presently lacks. Together, these reforms would improve the role of the FDA in the informational marketplace underlying physicians' prescribing decisions. This evolutionary extrapolation framework could also be applied to other contexts.*

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## INTRODUCTION

A recurring issue for evidence-based regulation of medicine is deciding whether to extend governmental approval from an existing use with sufficient current evidence of safety and efficacy to a novel use for which such evidence is currently lacking. This “extrapolation” issue can arise in four main contexts. First, “diagnosis extrapolation” occurs when physicians want to use an existing drug or device to treat a new condition (for example, using Seroquel to treat anxiety instead of schizophrenia). Second, “patient extrapolation” occurs when physicians want to use an existing drug or device to treat a new population with a given condition (for example, using Seroquel to treat children instead of adults). Third, “dosage extrapolation” occurs when physicians want to use an existing drug or device for a new duration or schedule of use, or at a new dosage (for example, using Seroquel indefinitely for schizophrenia when studies have only analyzed six weeks of use). Finally, “treatment extrapolation” occurs when physicians want to use a new drug or device that is related to an approved counterpart (for example, using extended-release Seroquel based on evidence that conventional Seroquel is safe and effective).<sup>1</sup>

The logic of preapproval testing, and the precautionary principle—first, do no harm<sup>2</sup>—would counsel toward prohibiting extrapolation approvals until *after* traditional safety and efficacy evidence exists with regard to the subjects that match the diagnostic class, patient class, dosage class, and treatment class. Yet the Food and Drug Administration’s (FDA’s) current regulations in many ways

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1. *Seroquel (Quetiapine Fumarate) Tablets: Full Prescribing Information*, ASTRAZENECA, available at <http://www1.astrazeneca-us.com/pi/Seroquel.pdf> (last visited Nov. 5, 2014).

2. HIPPOCRATES, OF THE EPIDEMICS bk. I, § 2(5) (Francis Adams trans., 2009).

reject the precautionary principle because they allow individual physicians to prescribe medications for off-label uses before any testing tailored to those uses has been done. This Article charts a course between the Scylla and Charybdis of the overly conservative precautionary principle on one hand, and the overly liberal FDA regime on the other. We instead propose a more dynamic and evolving evidence-based regime. Just as probationary hiring can be dynamically efficient in the employment context,<sup>3</sup> we argue that when ex ante due diligence is overly costly, a system that allows interim periods of use can provide physicians and patients greater treatment options while providing regulators with valuable evidence about the safety and efficacy of the proposed extrapolation. In contrast, a precautionary requirement—which would condition all approvals on pre-existing evidence for uses that constitute just slight extrapolations along any of these four dimensions—sacrifices probable short-term health benefits at the altar of precaution. Harm is not associated only with permitting access to unsafe products, but also with restricting access to beneficial products. The existing off-label regime captures the short-term benefits of extrapolation, but fails to sufficiently deter the long-term harms of perpetual prescribing into potentially hazardous off-label uses.

This Article instead calls for improvements in reporting, testing, and enforcement regulations to provide a more layered and dynamic system of regulatory incentives. The first element of our proposal is to improve the reporting of the amount and effect of off-label extrapolations through a more comprehensive reporting of off-label use (via the disclosure of diagnostic codes and “detailing” data) in manufacturers’ annual reports to the FDA, in the adverse event reports to the FDA, in Medicare/Medicaid reimbursement requests, and, for a subset of FDA-designated drugs, in the prescriptions themselves. The agency could then disseminate the de-identified information<sup>4</sup> it collects to allow third parties, such as academics,

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3. For a discussion, see generally Ian Ayres & Peter Siegelman, *The Q-Word as Red Herring: Why Disparate Impact Liability Does Not Induce Hiring Quotas*, 74 TEXAS L. REV. 1485 (1996); Ian Ayres, Colin Rowat & Nasser Zakariya, *Optimal Voting Rules for Two-Member Tenure Committees*, 36 SOC. CHOICE & WELFARE 323 (2011) (discussing academic tenure and, more generally, the practice of “up-or-out” hiring rules commonly found in law, business, and the military).

4. De-identified data has had individually identifiable health information removed so that it cannot be linked to a particular individual. Ryan Abbott, *Big Data and Pharmacovigilance: Using Health Information Exchanges to Revolutionize Drug Safety*, 99 IOWA L. REV. 225, 255 (2013).

insurers, pharmaceutical companies, and patient organizations, to complement its internal analyses. The second element of our proposal is the expansion of the FDA's utilization of postmarket testing requirements with regard to off-label drug use, and we provide a novel framework for evaluating whether postmarket testing is necessary.

Finally, the third element of our proposal is to create a tiered labeling system that would allow regulators and courts to draw finer reimbursement and liability distinctions. The FDA should create a category of "red box" warnings designed to completely prohibit certain off-label uses, require informed consent from patients for a subset of existing "black box" warnings, and create a category of "gray box" warnings to block Medicare Part D and Medicaid reimbursement by the Centers for Medicare and Medicaid Services (CMS). Our labeling system could also be used to motivate pharmaceutical companies to comply with postmarket testing requirements using both sticks (the threat of boxed warnings with the attendant risk of tort liability) and carrots (a category of "conditional off-label use" that would allow limited promotion). The improved reporting, testing, and enforcement regulations would work together to produce a more layered range of regulatory responses. The FDA, armed with better information about the extent of off-label use and its adverse effects, would be in a better position to require postmarket testing and to discourage off-label use with new types of warnings if manufacturers failed to provide sufficient, timely evidence of safety and efficacy in that particular extrapolation.

Our dynamic extrapolation approach is consonant with important parts of the FDA's current statutory authority, which calls on the agency to proactively respond to new sources of information and allows the FDA flexibility to require postmarket studies. Importantly, at least with regard to prescription drugs, our proposal could be entirely or largely adopted without the need for statutory amendment. Further, it should minimally strain the FDA's limited resources because it relies on informational regulation and market-based mechanisms to influence off-label prescribing practices.

In light of recent jurisprudence, the need for the agency to adapt in order to play a greater role in the informational marketplace that underlies physicians' prescribing decisions has never been more

critical. In 2012, in *United States v. Caronia*,<sup>5</sup> the Second Circuit stated that the Food, Drug, and Cosmetic Act (FDCA) does not prohibit truthful off-label promotion, and that such prohibitions would violate the First Amendment.<sup>6</sup> The Supreme Court expanded the protection afforded to advertising and marketing in the pharmaceutical field in *Thompson v. Western States Medical Center*<sup>7</sup> and *Sorrell v. IMS Health*.<sup>8</sup> These cases provide momentum for the industry's battle to secure increased First Amendment protection.<sup>9</sup> Our tiered labeling system, in contrast to agency prohibitions on manufacturer speech, is in line with the Brandeis notion that the remedy for bad speech is more speech.<sup>10</sup>

The FDA is also under pressure from strong consumerist objections to direct agency compulsion in connection with off-label use in clinical areas that tend to resist standardization, such as oncology. Our evolutionary evidence-based approach is also consonant with the general practice of allowing physicians to prescribe off-label uses in accordance with their professional judgment and knowledge. An optimal system would give physicians the flexibility to extrapolate on an individual level within reason, but would also ensure the collection of off-label experience data to be used for assessing whether the new-diagnostic, new-patient, new-dosage, or new-treatment extrapolation is warranted.

The remainder of this Article is divided into three parts. Part I provides background on current extrapolation practices surrounding three concerns: reporting, testing, and enforcement. Part II proposes reforms, and Part III uses the case studies of the drug Seroquel and the medical device Lap-Band to illustrate how this system might

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5. *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

6. *Id.* at 166–67.

7. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002). In *Thompson*, the Court held that it was unconstitutional for the FDA to prohibit pharmacies from advertising that they compounded specific drugs. *Id.* at 376–77.

8. *Sorrell v. IMS Health*, 131 S. Ct. 2653 (2011). In *Sorrell*, the Court held unconstitutional a Vermont statute that prohibited pharmaceutical companies from using prescriber-identifying information for marketing purposes. *Id.* at 2672.

9. Earlier, in *Washington Legal Foundation v. Friedman*, 13 F. Supp. 3d 51 (D.D.C. 1998), the court held that an FDA guidance restricting certain forms of manufacturer promotion of off-label uses imposed unconstitutional restrictions on commercial speech under the First Amendment. *Id.* at 74–75, *vacated as moot sub nom.* *Wash. Legal Found. v. Henney*, 202 F.3d 331, 336–37 (D.C. Cir. 2000).

10. “If there be time to expose through discussion the falsehood and fallacies, to avert the evil by the processes of education, the remedy to be applied is more speech, not enforced silence.” *Whitney v. California*, 274 U.S. 357, 377 (1927).

work. Although this Article focuses primarily on prescription drugs, the central elements of our framework apply to the regulation of medical devices, to over-the-counter drugs, and even to food safety. Indeed, as outlined in the Conclusion, our solution of evolutionary extrapolation can be seen as a type of Bayesian decisionmaking that is appropriate for a broad class of regulatory extrapolations that arise in a wide variety of legislative and rulemaking contexts.<sup>11</sup>

## I. WHY THE CURRENT REGIME IS INSUFFICIENTLY DYNAMIC

### A. Overview of the Approval Process

The Food and Drug Administration (FDA) is a federal regulatory agency within the Department of Health and Human Services (HHS) that approves and regulates drugs within the United States.<sup>12</sup> The FDA's primary mission is to protect the American public's health, which the agency accomplishes when it ensures that drugs and medical devices are safe and effective.<sup>13</sup> Within the FDA, the Center for Drug Evaluation and Research (CDER), the largest of the FDA's five centers, evaluates prescription and over-the-counter drugs' safety and efficacy through premarket approval and postmarket regulation.<sup>14</sup>

Premarket approval is a rigorous process that a drug must go through before the FDA will consider the drug to be safe and effective for human use. This premarket process has several stages. First, a product sponsor (a pharmaceutical company), having

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11. See generally SIMON JACKMAN, *BAYESIAN ANALYSIS FOR THE SOCIAL SCIENCES* (2009).

12. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 393 (2012).

13. *Id.* § 393(b)(1)–(4); see SUSAN THAUL, CONG. RESEARCH. SERV., R41983, *HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 1–2* (2012), available at <http://fas.org/sgp/crs/misc/R41983.pdf> (“[The] FDA also regulates products other than drugs—for example, biological products, medical devices, dietary supplements, foods, cosmetics, animal drugs, and tobacco products.”).

14. *How Drugs are Developed and Approved*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved> (last updated Oct. 23, 2014) (stating that “the other four FDA centers have responsibility for medical and radiological devices, food, and cosmetics, biologics, and veterinary drugs”); see THAUL, *supra* note 13, at 1–2 (“First, FDA reviews the safety and effectiveness of new drugs . . . this process is called *premarket approval* . . . . Second, once a drug has passed that threshold and is FDA-approved, FDA acts through its *postmarket* or *post-approval* regulatory procedures.”). For a simplified visual explanation of this process, see *Drug Approval Process*, U.S. FOOD & DRUG ADMIN. CTR. FOR DRUG EVALUATION & RESEARCH, available at <http://www.fda.gov/downloads/drugs/resourcesforyou/consumers/ucm284393.pdf> (last visited Nov. 5, 2014).

screened a drug for pharmacological activity and acute toxicity in animals, must submit an Investigational New Drug (IND) application to the FDA.<sup>15</sup> The FDA will review the IND and, if the agency is persuaded that clinical studies will not unreasonably place human subjects at risk, will authorize clinical trials.<sup>16</sup>

After completing clinical trials, the product sponsor can submit a formal application, known as a New Drug Application (NDA), to the FDA for marketing approval. Of the twenty therapeutic drugs approved in 2008, the median time for agency approval of an NDA was 10.9 months.<sup>17</sup> The median time from FDA authorization to initial testing in humans to market approval was 6.5 years.<sup>18</sup> If a drug passes the FDA's review process, the FDA will approve the drug for a particular indication in a specific population.

An NDA also contains proposed labeling that must be approved prior to marketing. This labeling is a summary of the evidence supporting the safe and effective use of the drug. The primary purpose of drug labeling is to give healthcare providers the necessary information for appropriate prescription, but patients may also find

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15. *Investigational New Drug (IND) Application*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm> (last updated Oct. 26, 2014).

16. Phase I trials are safety-focused: they typically involve “between 20 and 80” “healthy volunteers” and seek “to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects.” *Information for Consumers (Drugs): The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> (last updated May 28, 2014). In Phase II, the drug is tested on a larger group of between one hundred and three hundred individuals who “have the disease or condition that the product potentially could treat.” *Id.* Researchers continue to assess the drug's safety, but also begin evaluating its efficacy in treating the targeted disease or condition. *Id.* After Phase II, a drug is subjected to a balancing test of sorts: if the gravity of known risks to patients is outweighed by the efficacy of the drug and the severity of the disease it treats, the drug proceeds to Phase III. *Information for Consumers (Drugs): Inside Clinical Trials: Testing Medical Products in People, What is a Clinical Trial?*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm> (last updated Apr. 12, 2013). The third and usually final trial involves between one thousand and three thousand subjects with the targeted disease or condition, designed to gather data on safety, independent efficacy, side effects, and relative efficacy, as compared with other available treatments. *Id.*

17. Thomas J. Moore & Curt D. Furberg, *Development Times, Clinical Testing, Postmarket Follow-up, and Safety Risks for the New Drugs Approved by the US Food and Drug Administration: The Class of 2008*, 174 J. AM. MED. ASS'N INTERNAL MED. 90, 92 (2014).

18. *Id.*



drug labeling to be a source of useful information.<sup>19</sup> In recent years, the FDA has revised its labeling requirements to include more information and to be more accessible to physicians.<sup>20</sup> Drug labeling is an important risk-communication tool for the agency, as it alerts providers to, among other things, warnings and precautions, contraindications, adverse reactions, drug interactions, recommended use for specific populations, dosage, and administration.<sup>21</sup> In addition to standard warnings and precautions, labels may also include boxed or “black-box” warnings that alert prescribers to special risks.<sup>22</sup> “The warnings are separated (and thus highlighted) from other text in the package labeling by a prominent black-box border.”<sup>23</sup> Black-box warnings—the “highest level of all drug warnings promulgated by the FDA”<sup>24</sup>—may be required in a number of situations in which the FDA is aware of potentially high risks associated with the drug.<sup>25</sup>

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19. Mary E. Kremzner & Steven F. Osborne, *An Introduction to the Improved FDA Prescription Drug Labeling*, U.S. FOOD & DRUG ADMIN. (Nov. 23, 2010), <http://www.fda.gov/downloads/Training/ForHealthProfessionals/UCM090796.pdf>. For certain prescription drugs, the agency does require patient labeling, called Medication Guides or Patient Package inserts. *Id.*

20. *Id.*

21. *Id.*

22. The Code of Federal Regulations provides:

Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data . . . . The box must contain, in uppercase letters, a heading inside the box that includes the word “WARNING” and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the “Contraindications” or “Warnings and Precautions” section, accompanied by the identifying number for the section or subsection containing the detailed information.

21 C.F.R. § 201.57(c)(1) (2014); *see id.* § 201.57(c)(6)(i) (2014) (permitting the FDA to require black-box warnings relating to unapproved uses if “such usage is associated with a clinically significant risk or hazard”).

23. Karen E. Lasser, Diane L. Seger, Tony Yu, Andrew S. Karson, Julie M. Fiskio, Andrew C. Seger, Nidhi R. Shah, Tejal K. Gandhi, Jeffrey M. Rothschild & David W. Bates, *Adherence to Black Box Warnings for Prescription Medications in Outpatients*, 166 ARCHIVES INTERNAL MED. 338, 338 (2006).

24. Kylene Halloran & Paul G. Barash, *Inside the Black Box: Current Policies and Concerns with the United States Food and Drug Administration’s Highest Drug Safety Warning System*, 23 CURRENT OPINION ANESTHESIOLOGY 423, 423 (2010).

25. The FDA has stopped short of clearly articulating the criteria it uses in evaluating whether black-box warnings should be required, but it has identified three general situations in which such warnings would be appropriate:

1. There is an adverse reaction so serious in proportion to the potential benefit (for example, a fatal, life-threatening, or permanently disabling adverse reaction) that it must be considered in assessing the risks and benefits of using the drug.
2. There is a serious reaction that can be prevented or reduced in frequency or severity by patient selection, careful monitoring, avoiding certain concomitant

If the FDA determines safety measures are needed beyond the labeling, the agency can require the sponsor to develop a Risk Evaluation and Mitigation Strategies plan (REMS).<sup>26</sup> A REMS is required preapproval if the agency determines safety measures are needed beyond the professional labeling, and a REMS may also be required after a drug is approved if the agency becomes aware of new safety information.<sup>27</sup> No two REMS are identical: each REMS has unique safety measures designed to mitigate risks associated with a particular drug or class of drugs. A REMS may include a medication guide or patient package-insert requirement, a communication plan,

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therapy, addition of another drug, or managing the patient in a specific manner or avoiding use in a specific clinical situation.

3. The FDA approved the drug with restrictions on use and distribution to assure safe use.

U.S. FOOD & DRUG ADMIN. CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY: WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, AND BOXED WARNING SECTIONS OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS – CONTENT AND FORMAT (Oct. 2011), available at <http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf>.

26. “The Food and Drug Administration Amendments Act of 2007 (FDAAA) gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.” *Postmarket Drug Safety Information for Patients and Providers: Approved Risk Evaluation and Mitigation Strategies*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/drugsafety/postmarketdrug-safety-information-for-patients-and-providers/ucm111350.htm> (last updated Oct. 21, 2014). Prior to the FDAAA, the FDA used Risk Minimization Plans (RiskMaps) to influence physician and patient practices. RiskMaps are now integrated into the REMS regulatory infrastructure. *Postmarket Drug Safety Information for Patients and Providers: Isotretinoin (Marketed as Accutane) Capsule Information*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094305.htm> (last updated Oct. 22, 2010). Isotretinoin (Accutane) is a prominent example of a medicine with a robust RiskMap (iPledge) for pregnancy prevention in female patients. It has extensive requirements, such as monthly pregnancy tests, intended to prevent fetal exposure in patients taking isotretinoin. THE IPLEDGE PROGRAM, THE GUIDE TO BEST PRACTICES FOR THE IPLEDGE PROGRAM (Apr. 2012), available at <https://www.ipledgeprogram.com/Documents/Guide%20to%20Best%20Practices%20-%20iPLEDGE%20Program.pdf>. A sponsor report in February 2009 stated that forty physicians had been terminated from iPledge, primarily for misrepresenting information regarding patient gender and the date of the required pregnancy test. These discrepancies were largely reported by pharmacists and patients. Peggy Peck, *SDEF: FDA iPledge Program Sanctions 30 Physicians*, MEDPAGE TODAY (Feb. 13, 2009), <http://www.medpagetoday.com/MeetingCoverage/SDEF/12890>.

27. Some pharmaceutical companies submit a REMS voluntarily. U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, CTR. FOR BIOLOGICS EVALUATION & RESEARCH, GUIDANCE FOR INDUSTRY FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES, REMS ASSESSMENTS, AND PROPOSED REMS MODIFICATIONS 6 (Sept. 2009), available at <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>.

and elements to assure safe use (ETASU).<sup>28</sup> ETASU are the most extensive potential components of a REMS, and they set out actions that providers and organizations must take prior to prescribing or dispensing a drug, or, in some cases, as a condition of allowing a patient to continue treatment.<sup>29</sup> The ETASU may require special certification of practitioners, pharmacies, offices, and hospitals; may limit the settings in which a drug can be dispensed; or may mandate laboratory tests, registration, or other monitoring of individual patients.<sup>30</sup>

The FDA can also make approval conditional upon postmarketing requirements (PMRs) or postmarketing commitments (PMCs), which are studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use.<sup>31</sup>

### *B. The Off-Label Challenge—Balancing Access and Harm Prevention*

As a general matter, once a drug is approved, physicians may prescribe the drug without restriction.<sup>32</sup> Prescribing according to

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28. *Id.* at 5–6. REMS also require a timetable for sponsor submission to the agency of an assessment on the impact of a REMS. *Id.* at 5.

29. *Id.* at 6.

30. *Id.*

31. U.S. DEP'T OF HEALTH AND HUMAN SERVS. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, ADVANCES IN FDA'S SAFETY PROGRAM FOR MARKETED DRUGS: ESTABLISHING PREMARKET SAFETY REVIEW AND MARKETED DRUG SAFETY AS EQUAL PRIORITIES AT FDA'S CENTER FOR DRUG EVALUATION AND RESEARCH (Apr. 2012), <http://www.fda.gov/downloads/drugs/drugsafety/ucm300946.pdf>. PMRs are studies required by law, whereas PMCs are studies that are not legally required but that sponsors have agreed to conduct. Prior to the FDAAA, the FDA could require the following studies or clinical trials: "Postmarketing studies or clinical trials to demonstrate clinical benefit for drugs approved under the accelerated approval requirements in 21 CFR 314.510 and 21 CFR 601.41; Deferred pediatric studies (21 CFR 314.55(b) and 601.27(b)), where studies are required under the Pediatric Research Equity Act (PREA); Studies or clinical trials to demonstrate safety and efficacy in humans that must be conducted at the time of use of products approved under the Animal Efficacy Rule (21 CFR 314.610(b)(1) and 601.91(b)(1))." Since the FDAAA, postmarketing studies can be required to "[a]ssess a known serious risk related to the use of the drug", "[a]ssess signals of serious risk related to the use of the drug", and "[i]dentify an unexpected serious risk when available data indicate the potential for a serious risk." *Postmarketing Requirements and Commitments: Introduction*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments> (last updated Feb. 8, 2012).

32. See *CDRH Transparency: Overview of Medical Devices and Their Regulatory Pathways*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm203018.htm> (last updated Mar. 6, 2014)

FDA-approved parameters constitutes an on-label use, whereas the use of a drug outside those parameters constitutes an off-label use.<sup>33</sup> Off-label use is common: “for the 3 leading drugs in each of the 15 leading drug classes, off-label use account[s] for approximately 21% of prescriptions.”<sup>34</sup> Moreover, off-label uses may be the norm in some areas of practice, such as oncology, pain management, and palliative care, and in some patient populations, such as children, the elderly, and the severely ill.<sup>35</sup> For example, about 80 percent of all drug prescriptions for children are off-label, and between 80 and 90 percent of all drug prescriptions for rare diseases are off-label.<sup>36</sup>

The central problem with off-label use is that there is an information deficit. Whereas on-label use is based on scientifically valid and statistically significant evidence indicating that the potential benefits of a drug are likely to outweigh the potential risks, off-label use lacks such information. This is a serious problem because all approved drugs are potentially dangerous and have a risk of side effects, and patients should not be exposed to risk without evidence that a drug is likely to be effective. Unfortunately, the overwhelming

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(“The agency does not regulate the practice of medicine—how and which physicians can use a device.”); see also *Promotion of Unapproved Drugs and Medical Devices*, Testimony Before the S. Comm. on Labor and Human Res., 104th Cong. (1996) (statement of William B. Schultz, Deputy Comm’r for Policy, Food & Drug Admin.), available at <http://www.fda.gov/NewsEvents/Testimony/ucm115098.htm> (“The legislative history of the Federal Food, Drug, and Cosmetic Act indicates that Congress did not intend FDA to interfere with the practice of medicine. Thus, once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed in the FDA-approved labeling.”).

33. C. Lee Ventola, *Off-Label Drug Information: Regulation, Distribution, Evaluation, and Related Controversies*, 34 PHARMACY & THERAPEUTICS 428, 428 (2009); see also Randall S. Stafford, *Off-Label Use of Drugs and Medical Devices: A Review of Policy Implications*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 920, 920 (2012) (“‘Off-label use’ occurs when the use of a medication or device deviates from what is mentioned in its . . . FDA . . . product label.”).

34. Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008); see Chris Adams & Alison Young, *Prescribing Drugs “Off Label” Is Routine, but Can Injure, Kill Patients*, MCCLATCHY NEWSPAPER, Nov. 2, 2003, <http://www.mcclatchydc.com/2003/11/02/28121/prescribing-drugs-off-label-is.html> (explaining that prescriptions for off-label use nearly doubled over five years).

35. Marc A. Rodwin, *Rooting Out Institutional Corruption to Manage Inappropriate Off-Label Drug Use*, 41 J. L. MED. & ETHICS 654, 656 (2013).

36. James O’Reilly & Amy Dalal, *Off-Label or Out of Bounds: Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 324 (2003).

majority of off-label uses lack scientific support,<sup>37</sup> and thus, off-label prescribing may place “patients at risk of harm without adequate knowledge of the therapeutic risks and benefits.”<sup>38</sup> It has been estimated that about “15 percent of all drug uses lack scientific support for efficacy and more than 70 percent of off-label uses lack significant scientific support.”<sup>39</sup> In 2008, one study estimated that 67 percent of children treated with antipsychotic drugs were prescribed off-label treatments with an “uncertain” evidence base.<sup>40</sup> This is at odds with patients’ expectation that a drug’s safety and efficacy have been fully evaluated.<sup>41</sup> In fact, a recent poll of the U.S. public found that about half of respondents believed physicians were allowed to prescribe only for on-label indications, and about half believed physicians should be prohibited from off-label prescribing.<sup>42</sup> When off-label uses are not based on significant scientific data, the principles of evidence-based medicine argue that “intuition, unsystematic clinical experience, and pathophysiologic rationale are insufficient grounds for clinical decision making.”<sup>43</sup>

On the other hand, off-label drug use is a vital tool for patient care. It allows physicians to treat patients for whom off-label drug use may be the only therapy available, including patients for whom on-

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37. See Tewodros Eguale, David L. Buckeridge, Nancy E. Winslade, Andrea Benedetti, James A. Hanley & Robyn Tamblyn, *Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care*, 172 ARCHIVES INTERNAL MED., 781, 788 (2012); David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1026 (2006); see also Stafford, *supra* note 33, at 921 (“Off-label use without good evidence is common, particularly with respect to anticonvulsants (38% of all uses), allergy medications (31%), and psychiatric medications (29%).”).

38. Rodwin, *supra* note 35, at 654.

39. *Id.* at 656 (citing A. Brown, *Understanding Pharmaceutical Research Manipulation in the Context of Accounting Manipulation*, 41 J. L. MED. & ETHICS 611, 619 (2013)); Y. Feldman, R. Gauthier & T. Schuller, *Curbing Misconduct in the Pharmaceutical Industry: Insights from Behavioral Ethics and the Behavioral Approach to Law*, 41 J. L. MED. & ETHICS 620, 628 (2013).

40. G. C. Alexander, S. A. Gallagher, A. Mascola, R. M. Moloney & R. S. Stafford, *Increasing Off-Label Use of Antipsychotic Medications in the United States, 1995–2008*, 20 J. PHARMACOEPIDEMIOLOGY & DRUG SAFETY 177, 182 (2011).

41. See Stafford, *supra* note 33, at 2 (“Among its disadvantages, off-label use undercuts the public expectation that there has been a full evaluation of product safety and efficacy.”).

42. Harris Interactive, *U.S. Adults Ambivalent About the Risks and Benefits of Off-Label Prescription Drug Use* (Dec. 7, 2006), <http://www.harrisinteractive.com/NewsRoom/PressReleases/tabid/446/ctl/ReadCustom%20Default/mid/1506/ArticleId/986/Default.aspx>.

43. Gordon Guyat et al., *Introduction: The Philosophy of Evidence-Based Medicine, Users’ Guides to the Medical Literature*, 10 J. AM. MED. ASS’N 1, 4 (2002).

label use has failed.<sup>44</sup> Due to resource constraints, it will never be possible to study every possible drug for every possible off-label use, but drugs may nevertheless be safe and effective in many off-label contexts. For example, some drugs have been used widely for a long time with relatively few reported adverse events and with patients reporting benefit. Further, not all impressions of off-label use are based on anecdote; some off-label uses are supported by significant evidence, including from controlled clinical trials. When high-quality research on off-label use precedes FDA approval, early physician adoption can improve patient outcomes.<sup>45</sup> Compendia, such as the *American Hospital Formulary Service Drug Information*, evaluate and disseminate evidence supporting off-label uses.<sup>46</sup> In fact, Medicare Part D and other drug plans may base the reimbursement of off-label uses on their inclusion in major drug compendia.<sup>47</sup>

Off-label drug use impacts more than individual patient care—it may also serve as a pathway to innovation. Off-label drug use can provide valuable data about the effects of the drug for different conditions and populations, and this data can then be used to inform future clinical practice.<sup>48</sup> In essence, it has the capacity to create a clinical laboratory. Unfortunately, despite widespread use of off-label prescribing, patient outcomes are generally not evaluated in a consistent and transparent manner.<sup>49</sup> Also, when drugs are prescribed for off-label uses, healthcare costs may increase.<sup>50</sup> The cost of

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44. Stafford, *supra* note 33, at 921.

45. *Id.*

46. *American Hospital Formulary Service Drug Information*, AM. SOC'Y OF HEALTH-SYS. PHARMACISTS, <http://www.ashp.org/ahfs> (last visited Nov. 5, 2014).

47. R. Dresser & J. Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J. L. MED. & ETHICS 476, 480 (2009). A recent review of Medicare-approved compendia governing reimbursement for off-label oncological uses, however, reported that the compendia were “lacking in consistency, quality, transparency, and timeliness.” *Id.* at 479.

48. *Id.*

49. Marc A. Rodwin, *Conflicts of Interest, Institutional Corruption, and Pharma: An Agenda for Reform*, 40 J. L. MED. & ETHICS 511, 515–16 (2012); see also Benjamin Falit, *The Path to Cheaper and Safer Drugs: Revamping the Pharmaceutical Industry in Light of GlaxoSmithKline's Settlement*, 33 J. L. MED. & ETHICS 174, 179 (2005) (explaining that after initial FDA approval, “pharmaceutical companies [are] responsible for informing physicians about the safety of their drugs”).

50. Off-label use is widely thought to increase healthcare costs because it increases spending on drugs. See Stafford, *supra* note 33, at 3. Increased spending on drugs may increase healthcare costs regardless of whether patient outcomes improve. *Id.* On the other hand, it may be possible for off-label use to decrease healthcare costs if it is less expensive than an alternate

prescription drugs is a significant driver of the cost of healthcare in the United States.<sup>51</sup> For example, of the twelve anti-cancer drugs approved by the FDA in 2012, eleven of them cost over \$100,000 a year.<sup>52</sup> Finally, off-label use disincentivizes companies from conducting additional clinical research because it allows them to sell their products without seeking FDA approval.<sup>53</sup> Under the current regulatory regime, manufacturers opt for back-door approaches to developing off-label revenue streams because of the “enormous amount of time and money”<sup>54</sup> required to seek FDA approval for a new use.

Pharmaceutical companies have a significant impact on physicians’ off-label prescribing practices.<sup>55</sup> Although companies are prohibited from directly promoting off-label drug use,<sup>56</sup> the FDA

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treatment. Off-label use may also decrease costs by improving health outcomes, resulting in reduced need for future treatment.

51. Ryan Abbott, *Treating the Health Care Crisis: Complementary and Alternative Medicine for PPACA*, 14 DEPAUL J. HEALTH CARE L. 35, 57 (2011).

52. Experts in Chronic Myeloid Leukemia, *The Price of Drugs for Chronic Myeloid Leukemia (CML) is a Reflection of the Unsustainable Prices of Cancer Drugs: From the Perspective of a Large Group of CML Experts*, 121 J. BLOOD 4439, 4439 (2013).

53. See Stafford, *supra* note 34, at 1427–28.

54. Ventola, *supra* note 33, at 431; see also Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 237 (2011) (explaining that “[t]hese conditions disincentivize manufacturers from seeking formal FDA review of all but the most potentially lucrative of off-label uses, and the ones most likely to be granted approval”).

55. Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 J. AM. MED. ASS’N 373, 373–80 (2000). As David Kessler wrote while he was the Commissioner of the FDA,

Prescription drug advertisements sometimes distort information in ways that may be difficult to detect by even the trained observer. Unless the individual physician is an expert in the particular disease or therapeutic class linked to the drug advertisement, it is unlikely he or she will engage in a critical analysis of the evidence supporting every new drug claim . . . .

David A. Kessler, *Addressing the Problem of Misleading Advertising*, 116 ANNALS INTERN. MED. 950, 950 (June 1, 1992).

56. Ventola, *supra* note 33, at 428. Within the FDA, the Office of Prescription Drug Promotion (OPDP) evaluates proposed and effective drug and device promotions—advising sponsors who submit draft materials as well as identifying violations. *The Office of Prescription Drug Promotion (OPDP)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm>. The OPDP is charged with addressing the promotion of off-label drug use, but does not typically regulate nonpromotional activities and events, the dissemination of scientific material, or the exchange of information, unless it appears they are sponsor-backed. See 21 C.F.R. § 314.81(b)(3)(i) (2014). The OPDP relies heavily on voluntary submissions by pharmaceutical companies, supplemented by limited monitoring and surveillance. *Id.* Violations of marketing regulations can result in steep fines and penalties. *Id.*

allows them to give physicians information about off-label drug uses from journal articles and reference publications.<sup>57</sup> This primarily occurs during face-to-face sales and promotional activities, referred to as “detailing.”<sup>58</sup> As the Supreme Court noted in *IMS v. Sorrell*, “[p]harmaceutical manufacturers promote their drugs to doctors through a process called ‘detailing.’ . . . Detailers bring . . . medical studies that explain the ‘details’ and potential advantages of various prescription drugs. Interested physicians listen, ask questions, and receive follow-up data.”<sup>59</sup> Companies spend a substantial amount on detailing and similar marketing activities—more than \$27 billion in 2012.<sup>60</sup> Of that amount, about \$24 billion was spent on advertising to physicians and \$3 billion was spent on direct marketing to consumers (primarily on television advertisements).<sup>61</sup> Moreover, evidence suggests that pharmaceutical companies often violate prohibitions on off-label promotion.<sup>62</sup>

Private and public insurers also have a significant influence on off-label use. Patients who cannot independently cover the cost of prescription medicines will not be able to engage in off-label use without insurance-cost sharing. Insurers also have a financial incentive to limit off-label use to the extent they believe it will increase overall costs.<sup>63</sup> Private insurers have attempted to restrict prescribing practices by arguing that such prescriptions are not “medically necessary,” but this tactic has met with limited success.<sup>64</sup>

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57. The agency suggests that companies follow Good Reprint Practices. U.S. FOOD & DRUG ADMIN., GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (2009), [www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm).

58. CEGEDIM STRATEGIC DATA, 2012 U.S. Pharmaceutical Company Promotion Spending (2013), [http://www.skainfo.com/health\\_care\\_market\\_reports/2012\\_promotional\\_spending.pdf](http://www.skainfo.com/health_care_market_reports/2012_promotional_spending.pdf).

59. *IMS v. Sorrell*, 132 S. Ct. 2653, 2656–57 (2011) (citations omitted). “Similar efforts to promote the use of generic pharmaceuticals are sometimes referred to as ‘counter-detailing.’” *Id.* at 2661.

60. See CEGEDIM STRATEGIC DATA, *supra* note 58, at 2.

61. *Id.*

62. Aaron S. Kesselheim, David M. Studdert & Michelle M. Mello, *Whistle-Blowers’ Experiences in Fraud Litigation against Pharmaceutical Companies*, 362 NEW ENG. J. MED. 1832, 1833 tbl. 1 (2010); Michelle M. Mello, David M. Studdert & Troyen A. Brennan, *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 1557, 1566 (2009).

63. Ryan Abbott & Carl Stevens, *Redefining Medical Necessity: A Consumer Driven Solution to the U.S. Health Care Crisis*, 32 LOY. L. REV. (forthcoming 2014).

64. *Id.*; see Ventola, *supra* note 33, at 435 (detailing insurers’ arguments against off-label prescribing). Many courts have adopted a *contra preferentem* approach in challenges to insurers’



The primary public insurer, CMS, generally does not reimburse for off-label uses in the Medicare/Medicaid context, except for off-label uses that are recognized as effective in various compendia.<sup>65</sup> However, a 2009 survey of third-party payers administering Medicare/Medicaid drug benefits found vast discrepancies in reimbursement policies for off-label use.<sup>66</sup> One-quarter of administrators reported that they simply did not reimburse off-label prescriptions, while 15 percent reported that they were unable to utilize effective policies covering off-label use because it was too difficult for them to detect.<sup>67</sup> Among administrators reimbursing for off-label prescriptions, over half had restrictions requiring some combination of insurer preauthorization, limiting reimbursement to certain indications, requiring therapeutic alternatives prior to off-label use, limiting quantities of off-label prescriptions, and requiring enhanced beneficiary cost sharing.<sup>68</sup>

Beyond the FDA, industry, and insurers, there are only a few significant influences on off-label prescribing. States regulate prescribing only insofar as to prevent fraud, avert overdose, and set practices for state benefits programs.<sup>69</sup> Healthcare institutions, such as

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attempts to limit off-label or experimental use. Under this approach, off-label uses are covered unless expressly and clearly excluded by the insurance contract. In *Lubeznik v. HealthChicago*, 644 N.E.2d 777 (Ill. App. Ct. 1994), a patient with advanced ovarian cancer obtained an injunction requiring her insurance company to pre-certify her for a debatably experimental treatment. *Lubeznik v. HealthChicago*, 644 N.E.2d 777, 778, 780 (Ill. App. Ct. 1994). The primary source of data used to assess the procedure was the treating physician, who claimed to have performed twenty-one such procedures with a 75 percent success rate. *Id.* at 779. “In 1993, a California jury awarded \$89 million in damages against an insurer that had refused to cover ABTM, including \$77 million in punitive damages.” BARRY R. FURROW ET AL., *HEALTH LAW: CASES, MATERIALS AND PROBLEMS* 643 (7th ed. 2013). Eventually, thirty thousand women received the same treatment at a cost of \$3 billion. *Id.* at 644. Fewer than ten years after Bonnie Lubeznik’s landmark case against the insurer was decided in her favor, studies proved the treatment had no beneficial effects. *Id.*

65. See Compendia for Determination of Medically-Accepted Indications for Off-Label Uses of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen, 42 C.F.R. § 414.930 (2014). Compendia summarize and evaluate the evidence supporting off-label uses. Dresser & Frader, *supra* note 47, at 479. However, these evaluations are not as rigorous as FDA review. *Id.* Compendia have been criticized as lacking in consistency, quality, transparency, and timeliness. Katherine Tillman, Brijet Burton, Louis B. Jacques & Steve E. Phurrough, *Compendia and Anticancer Therapy Under Medicare*, 150 ANNALS INTERN. MED., 348, 348–49 (2009).

66. J. Cohen, A. Wilson & L. Faden, *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 394 (2009).

67. *Id.*

68. *Id.*

69. CTRS. FOR DISEASE CONTROL & PREVENTION, *Law: Prescription Limits*, [http://www.cdc.gov/HomeandRecreationalSafety/Poisoning/laws/rx\\_limits.html](http://www.cdc.gov/HomeandRecreationalSafety/Poisoning/laws/rx_limits.html) (last visited Nov. 5, 2014). There are exceptions—for example, states such as Ohio and Oklahoma have

Kaiser and the Veteran's Administration, may have restrictions or internal protocols regarding off-label use, but these apply only internally. Medical associations may make recommendations regarding best practices or clinical guidelines, but otherwise do not censor or participate in assessing prescribing habits, especially on the level of individual patients. Finally, tort liability acts as a constraint on physicians' prescribing practices to the extent that off-label prescribing can generate malpractice liability if it fails to adhere to accepted standards of care.<sup>70</sup>

### C. *The FDA's Postmarket Regulation*

The FDA has various tools for postmarket regulation: reporting requirements, agency surveillance, warnings, and postmarket trial requirements for pharmaceutical companies. Product sponsors are required to submit postmarket reports of all serious and unexpected adverse reactions to the FDA's Adverse Events Reporting System (AERS)<sup>71</sup> within fifteen days of becoming aware of the event.<sup>72</sup> Physicians and patients are not required to report adverse events, but may report adverse reactions voluntarily to the FDA's MedWatch<sup>73</sup> reporting system, the data from which is incorporated in the AERS database.<sup>74</sup> Pharmaceutical companies are also required to report the results of any postmarket clinical trials and findings from their own and others' research and publications.<sup>75</sup>

The FDA's CDER and Office of Surveillance and Epidemiology analyze data submitted by manufacturers, physicians, and patients after a drug goes on the market. Agency scientists examine reported

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required (or have attempted to require) that mifepristone, or abortifacients generally, be used on-label. Irin Carmon, *Court Blocks Arizona Abortion Restrictions*, MSNBC (June 3, 2014, 3:55 PM), <http://www.msnbc.com/msnbc/court-blocks-arizona-abortion-restrictions>.

70. S.R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 194 (1999).

71. *Drug Approvals and Databases: Adverse Event Reporting System (AERS)*, U.S. FOOD & DRUG ADMIN, <http://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm> (last updated Sept. 17, 2014). For additional information about AERS, see *Adverse Event Reporting System (FAERS) (formerly AERS)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last updated Sept. 8, 2014) (discussing problems with data in the FAERS system).

72. Records and Reports Concerning Adverse Drug Experiences on Marketed Prescription Drugs for Human Use Without Approved New Drug Applications, 21 C.F.R. § 310.305 (2014).

73. *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/MedWatch> (last updated Oct. 25, 2014).

74. THAUL, *supra* note 13, at 11.

75. *Id.* at 12; see 21 U.S.C. § 355(k) (2012) (describing records and reporting requirements).

data to determine which adverse reactions are related to the drug.<sup>76</sup> Although the present system is largely passive, relying on third-party reports submitted to the agency, the FDA “has started to develop an infrastructure that uses data from public and private sources . . . and expands its information base.”<sup>77</sup> Through the new, more active surveillance system, the Sentinel Initiative, the FDA aims to “better detect safety signals, analyze data to understand them, and identify strategies to fix the problem.”<sup>78</sup> The Sentinel Initiative now has the capacity to monitor adverse events in over one hundred million U.S. residents by actively querying diverse automated healthcare-data holders—including electronic medical-record systems, insurance-claims databases, and registries.<sup>79</sup>

The FDA can mandate drug-label changes to warn physicians and patients when the agency becomes aware of new safety information that it determines should be included in the labeling.<sup>80</sup> Such changes range from requiring pharmaceutical companies to update warnings and precautions, to imposing a black-box warning. Although boxed warnings may be required at the time of FDA approval, they are more commonly added after a drug has been approved and the FDA has received reports of adverse effects.<sup>81</sup>

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76. THAUL, *supra* note 13, at 12.

77. *Id.* at 13.

78. *Id.*; see *Sentinel Initiative—Transforming How We Monitor Product Safety: FDA’s Sentinel Initiative—Ongoing Projects*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm203500.htm> (last updated July 11, 2012) (describing the “scientific operations needed for the Sentinel Initiative”); *FDA’s Sentinel Initiative*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm> (last updated Oct. 22, 2014) (providing an overview of the Sentinel Initiative); *Sentinel Initiative—Transforming How We Monitor Product Safety: Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm089474.htm> (last updated Feb. 24, 2010) (detailing the Sentinel Initiative); U.S. FOOD & DRUG ADMIN, SENTINEL INITIATIVE, <http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM124701.pdf> (last visited Nov. 5, 2014) (same).

79. See sources cited *supra* note 78.

80. 21 U.S.C. § 355(o)(4) (2012); see U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES—IMPLEMENTATION OF SECTION 505(o)(4) OF THE FD&C ACT (2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf> (discussing the FDA’s thoughts on how the regulation and the statutory provision relate to one another in the safety-labeling-changes guidance).

81. NORMAN S. MARKS & KAREN WEISS, BOXED WARNINGS AND OTHER FDA COMMUNICATION TOOLS 259 (2010), available at <http://www.fda.gov/downloads/Safety/MedWatch/UCM201430.pdf>.

In 2007, Congress substantially expanded the FDA's ability to require postmarket studies under the Food and Drug Administration Amendments Act (FDAAA).<sup>82</sup> The agency can now demand PMRs to assess a known serious risk, to assess signals of a serious risk, or to identify an unexpected serious risk.<sup>83</sup> After drug approval, the agency needs new safety information to demand a PMR.<sup>84</sup> Congress's passage of the FDAAA was a direct and powerful response to reported "inadequacies in drug companies' fulfillment of . . . postmarketing studies and weaknesses in FDA's regulatory authority to enforce these commitments."<sup>85</sup> As the breadth of the statutory language suggests, the FDAAA "envisions heavy use, during the postmarket period, of large observational studies that rely on interoperable health data networks."<sup>86</sup> Indeed, this authorization represented the most transformative amendment to the FDCA in the last fifty years.<sup>87</sup> It has been characterized as "a sweeping overhaul of . . . both the FDCA and the Public Health Service Act"<sup>88</sup> and "a profound change in law."<sup>89</sup> Before the FDAAA, the FDA could only request that pharmaceutical companies conduct postmarket testing.<sup>90</sup>

As a final step, the FDA has the authority to revoke marketing authorization and remove a drug from the market. Four percent of approved drugs are eventually removed.<sup>91</sup>

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82. Jill Wechsler, *FDAAA Empowers FDA To Have Greater Control over Drug Safety*, FORMULARY WATCH (Dec. 1, 2007), <http://formularyjournal.modernmedicine.com/formulary-journal/news/clinical/clinical-pharmacology/fdaaa-empowers-fda-have-greater-control-over-d>.

83. The Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, § 901(a) (codified in scattered sections of 21 U.S.C.).

84. *Id.*

85. Kevin Fain, Matthew Daubresse & G. Caleb Alexander, *The Food and Drug Administration Amendments Act and Postmarketing Commitments*, 310 J. AM. MED. ASS'N 202, 202 (2013) (citing a 2006 report by the Office of Inspector General).

86. Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 420–21 (2010).

87. *See id.* at 422–23 (discussing the history of amendments to the FDCA and characterizing the FDAAA as "the most momentous shift in drug regulation in half a century").

88. David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts To Preempt Failure-To-Warn Claims*, 96 GEO. L. J. 461, 467 (2008).

89. Evans, *supra* note 86, at 422.

90. U.S. FOOD & DRUG ADMIN., ADVANCES IN FDA'S SAFETY PROGRAM FOR MARKETED DRUGS: ESTABLISHING PREMARKET SAFETY REVIEW AND MARKETED DRUG SAFETY AS EQUAL PRIORITIES AT FDA'S CENTER FOR DRUG EVALUATION AND RESEARCH (2012), <http://www.fda.gov/downloads/drugs/drugsafety/ucm300946.pdf>.

91. Abbott, *supra* note 4, at 228 n.9.

#### D. Problems with FDA Postmarket Regulation

Evidence suggests that the FDA is not yet optimally regulating off-label and postmarket drug use despite its expanded statutory mandate.<sup>92</sup> Notwithstanding expectations that the FDA would use its enhanced regulatory power under the FDAAA to more aggressively police postmarket drug use, the agency has demonstrated reluctance to realize the ambitious statutory mandate envisioned by Congress. The FDA has required relatively few postmarket studies and has allowed manufacturers to drag their feet in responding to the requests that the FDA has submitted.<sup>93</sup> For example, a 2014 study found that the FDA had required eighty-five PMCs for the twenty therapeutic drugs approved in 2008, but that only twenty-six had been fulfilled, and only eight had been submitted for agency review.<sup>94</sup> In addition, a 2013 report by the Office of the Inspector General concluded that the agency had failed to consistently enforce REMS requiring ETASU. The FDA approved 199 REMS between 2008 and 2011.<sup>95</sup> However, FDA review memoranda of forty-nine recent sponsor assessments of

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92. “Congress has enacted legislation to expand the FDA’s authority with the intent of protecting the public health but often without appropriating the necessary resources.” Raymond L. Woosley, *One Hundred Years of Drug Regulation: Where Do We Go from Here?*, 53 ANNUAL REV. PHARMACOLOGY & TOXICOLOGY 255, 265 (2013). That was in the best of times. The federal shutdown in October 2013 “left US public health systems reeling and exposed their vulnerability to national politics.” Bridget M. Kuehn, *Shutdown Underscored Vulnerability of US Public Health and Biomedical Research to Political Wrangling*, 310 J. AM. MED. ASS’N. 1907 (2013). About half of the FDA’s staff were furloughed. U.S. DEP’T OF HEALTH AND HUMAN SERVS., CONTINGENCY STAFFING PLAN FOR OPERATIONS IN THE ABSENCE OF ENACTED ANNUAL APPROPRIATIONS (2013), [http://www.hhs.gov/budget/fy2014/fy2014contingency\\_staffing\\_plan-rev6.pdf](http://www.hhs.gov/budget/fy2014/fy2014contingency_staffing_plan-rev6.pdf).

93. See Howard Bauchner & Phil B. Fontanarosa, Editorial, *Restoring Confidence in the Pharmaceutical Industry*, 309 J. AM. MED. ASS’N 607, 608 (2013) (explaining that “an important proportion of these [postmarket] studies are not completed in a timely fashion” and lamenting that “[w]ithout rigorous postmarketing studies, the true risk and safety profile of a drug in the ‘real-world’ patient population is not defined”); Fain et al., *supra* note 85, at 202–03 (analyzing the FDA’s use of postmarket studies from 2007 and 2011 and concluding that this “analysis reinforces continued concerns about the status of prescription drug postmarketing studies in the United States”).

94. Thomas J. Moore & Curt D. Furberg, *Development Times, Clinical Testing, Postmarket Follow-up, and Safety Risks for the New Drugs Approved by the US Food and Drug Administration: The Class of 2008*, 174 J. AM. MED. ASS’N INTERNAL MED. 90, 90 (2014). (“None of the trials conducted prior to approval assessed the efficacy of the drug beyond 24 weeks, including for those medications intended for open ended use.”).

95. OFFICE OF INSPECTOR GEN., DEP’T OF HEALTH & HUMAN SERVS., FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY, No. OEI-04-11-00510, at 11 (2013).

REMS showed that only seven met all requirements.<sup>96</sup> Of the sponsor assessments, “nearly half . . . did not include all information requested in FDA assessment plans,” and ten were late.<sup>97</sup>

Although current labeling practices, including boxed warnings, have been shown in some studies to decrease prescriptions and sales of certain drugs,<sup>98</sup> these warnings have been widely criticized as ineffective<sup>99</sup> and arbitrary.<sup>100</sup> Indeed, one study found that more than 40 percent of ambulatory-care patients received at least one potentially relevant black-box warning medication in a thirty-month period, and that compliance with black-box warnings was “highly variable.”<sup>101</sup> Another observational study of fifty-one outpatient practices using an electronic health record looked at a total of 324,548 patients and found that 33,778 of them (10.4 percent) received a medication with a black-box warning. In 7 percent of those cases, the prescribing physician violated the black-box warning.<sup>102</sup> Despite the specificity of their labeling requirements, black-box warnings have arguably failed to prevent the potentially dangerous drug uses they were designed to target. Instead, they have engendered confusion and controversy among prescribers. This warning system is at once too inflexible in demanding a binary distinction between one small set of

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96. *Id.*

97. *Id.*

98. *See, e.g.*, E. Ray Dorsey, Sarah A. Gallagher, Rena M. Conti & G. Caleb Alexander, *Impact of FDA Black Box Advisory on Antipsychotic Medication Use*, 170 ARCHIVES INTERNAL MED. 96, 100 (2010) (finding that the FDA’s April 2005 advisory and black-box warning requirements concerning the increased risk of mortality associated with the use of certain antipsychotics among elderly patients “was associated with a decrease in the use of the medications,” and that this decline lasted more than two years).

99. *See, e.g.*, Anita K. Wagner, K. Arnold Chan, Inna Dashevsky, Marsha A. Raebel, Susan E. Andrade, Jennifer Elston Lafata, Robert L. Davis, Jerry H. Gurwitz, Stephen B. Soumerai & Richard Platt, *FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full?*, 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 369, 370–74 (2006) (characterizing black-box warnings’ “effectiveness as a risk communication tool” as “debatable” and identifying the “need for better methods of ensuring the safe use of medications that are considered to carry serious risks”).

100. *See, e.g.*, Halloran & Barash, *supra* note 24, at 424 (“The nonspecific and arguably unscientific methods by which a drug receives a [black-box warning], in addition to biases of committee members making critical decisions regarding the fate of dangerous drugs, have cast doubt on the quality of the system.”); *see generally* Bryan A. Liang, Editorial, *FDA Use of the Black Box Warning: Time for Reevaluation as a Safety Tool*, 14 J. CLINICAL ANESTHESIA 561 (2003) (lamenting the FDA’s failure to provide specific guidance regarding the conditions under which black-box warnings may be required).

101. Wagner et al., *supra* note 99, at 374.

102. Lasser et al., *supra* note 23, at 340.

drug uses and all others and too feeble in failing to impose significant costs on those who ignore it.

## II. DESIGNING AN EVOLUTIONARY, EVIDENCE-BASED EXTRAPOLATION REGULATION

### A. *Improved Data Collection*

The starting point for our proposal is to improve reporting of off-label drug use in the United States. Although we are by no means the first to identify the problems with our current reporting regime in this area,<sup>103</sup> we believe that the benefits of integrating and consolidating existing information regarding off-label use are greater today than ever before and, indeed, may be achieved through a combination of several modest tweaks to existing policies.<sup>104</sup> Specifically, we believe that five concrete and politically achievable policy changes would dramatically improve the quality and quantity of information available regarding off-label use: (1) requiring greater manufacturer reporting of off-label use, (2) including diagnostic codes in adverse event reporting, (3) including diagnostic codes in Medicare/Medicaid reimbursement requests, (4) requiring diagnostic use at the point of prescription for a subset of FDA-designated drugs, and (5) disseminating publicly the de-identified collected data.

1. *Manufacturer Reporting of Off-Label Use.* First, we recommend that manufacturers be required to provide the FDA with

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103. See, e.g., Stafford, *supra* note 34, at 1427–29 (identifying the absence of consistent, detailed reporting on off-label drug use); Surrey M. Walton, Glen T. Shumock, Ky-Van Lee, G. Caleb Alexander, David Meltzer & Randall S. Stafford, *Prioritizing Future Research on Off-Label Prescribing: Results of a Quantitative Evaluation*, 28 PHARMACOTHERAPY 1443, 1450 (2008) (“Policy surrounding data collection, coding, and the prescription mechanism need to be updated, particularly in the current environment where many health systems are moving to electronic health records and electronic prescribing.”).

104. When Congress amended the FDA’s statutory mandate in 2007, the FDA expressed a keen awareness of the potential benefits from improving communication and enhancing its data-collection systems. The FDA explained, for example, that “[i]mproving our communication and information flows will further strengthen the effectiveness of the drug safety system.” 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* 12 (2007). Our proposal takes the FDA at its word and suggests that this objective may be achieved through a combination of relatively minor changes in the reporting requirements of various actors in the off-label-drug market.

annual reports on the off-label uses of their drugs.<sup>105</sup> These reports would provide a rough breakdown of each approved drug's annual sales by diagnostic code, thus allowing the FDA to identify the diagnoses for which each of its approved drugs was being used in the United States. This type of reporting requirement may seem onerous at first blush but, in fact, would do little more than require manufacturers to disclose the information they already have—indeed, the same information that allows them to turn handsome profits from off-label use.<sup>106</sup> Manufacturers acquire this information from a variety of sources; for example, they purchase data on off-label use from companies that aggregate data on physicians' prescribing practices.<sup>107</sup> This data represents a vital component of the detailing process, as it is used to refine marketing tactics and to increase sales.<sup>108</sup>

Manufacturers are also, as many commentators have pointed out, intimately involved in the development of peer-reviewed research documenting the off-label uses of their drugs.<sup>109</sup> To cite only

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105. This information is not currently required of manufacturers, which are required to submit reports only on adverse events. 21 C.F.R. § 314.80 (2014).

106. As the FDA has explained,

[s]cientific or medical departments within drug or medical device firms often maintain a large body of information about their products. This information typically includes data and other information consistent with the approved or cleared indications or conditions of use for their products, but may also include off-label information for their products.

U.S. DEP'T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN, GUIDANCE FOR INDUSTRY RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND MEDICAL DEVICES (Dec. 2011), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf>.

107. Although physicians are not required to detail the diagnostic codes of off-label treatments, they often choose to do so, and commentators have noted that the cost of providing diagnostic codes has decreased substantially in recent years. *See, e.g.*, Walton et al., *supra* note 103, at 1450 (explaining that although “physicians are not required to document the indication for which a drug is prescribed . . . [d]ocumentation of a diagnosis for each drug prescribed is likely to be increasingly useful and feasible [and] at the same time could reduce medication errors”).

108. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2657 (2011).

109. *See, e.g.*, Ventola, *supra* note 33, at 430 (discussing manufacturers' ability to “conduct the clinical trials that are necessary to gain regulatory approval and then disseminate these data through marketing, advertising, and publication in the medical literature”). The involvement of manufacturers in developing the literature supporting the efficacy of certain off-label uses has only increased, according to several commentators, since the FDA began allowing manufacturers to distribute reprints of this literature in 2009. *See, e.g.*, Kesselheim, *supra* note 54, at 256 (discussing the ability of manufacturers to “pass out medical journal article reprints that discuss off-label uses without the off-label use being the subject of an [FDA investigation]”); Mello et al., *supra* note 62, at 1559 (discussing manufacturers' historical ability to distribute peer-reviewed literature on off-label uses and noting the effects of the FDA's 2009 guidance on this practice).



a few of the most public (and controversial) examples, the manufacturer of one hemostatic agent approved for the treatment of hemophilia “played a substantial role in sponsoring, designing, directing, analyzing, and publishing much of the . . . evidence” supporting the drug’s off-label use;<sup>110</sup> Eli Lilly sponsored and developed a series of articles appearing in publications such as the *New England Journal of Medicine* regarding the off-label use of its drug, recombinant human activated protein C (Xigris);<sup>111</sup> and Allergan, the manufacturer of Botox, has recently pointed to studies demonstrating the efficacy of off-label uses of its drug—uses that now support nearly half of the drug’s sales.<sup>112</sup> In examples such as these, manufacturers’ knowledge of off-label uses has supported a significant portion—and in some cases a majority—of their drugs’ sales, yet manufacturers have no obligation to share this knowledge with the FDA.<sup>113</sup> Although third-party researchers have been able to provide a rough picture of off-label use by relying on various datasets,<sup>114</sup> the manufacturers themselves remain free to withhold the information that frequently winds up printed in ghost-written, peer-reviewed articles and that ultimately supports a significant source of their revenue.<sup>115</sup> Requiring manufacturers to provide the FDA with

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110. Veronica Yank et al., *Systematic Review: Benefits and Harms of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications*, 154 ANNALS INTERN. MED. 529, 537 (2011).

111. See ROSS MCKINNEY, AMY P. ABERNETHY, DAVID B. MATCHAR & JANE L. WHEELER, POTENTIAL CONFLICT OF INTEREST IN THE PRODUCTION OF DRUG COMPENDIA 10 (2009).

112. See Jef Feeley & Phil Milford, *Allergan Holders Can Proceed with Botox Suit, Judge Rules*, BLOOMBERG (June 11, 2012, 3:19 PM), <http://www.bloomberg.com/news/2012-06-11/allergan-holders-can-proceed-with-botox-suit-judge-rules-1-.html>.

113. See, e.g., Kesselheim, *supra* note 54, at 235–36 (explaining that nearly 75 percent of one oncology drug’s use was off-label); Tracy Staton, *Allergan Inks \$600M Off-Label Settlement*, FIERCEPHARMA (Sept. 2, 2010), <http://www.fiercepharma.com/story/allergan-inks-600m-label-settlement/2010-09-02> (providing examples of manufacturers prioritizing off-label drug use).

114. See, e.g., Radley et al., *supra* note 37, at 1025 (estimating the prevalence of off-label prescriptions by using the 2001 National Disease and Therapeutic Index, which the authors characterize as “a nationally representative survey of office-based physicians”); see also Walton et al., *supra* note 103, at 1445 (discussing researchers’ ability to “quantif[y] the volume of off-label uses for a specific drug by using the National Disease and Therapeutic Index”); S.M. Walton, W.L. Galanter & D. Sarne, *A Trial of Inpatient Indication Based Prescribing During Computerized Order Entry with Medications Commonly Used Off-Label*, 2 APPLIED CLINICAL INFO. 94 (2011), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631908> (conducting a clinical study to estimate the magnitude of off-label use of certain drugs).

115. Sergio Sismondo, *Ghosts in the Machine: Publication Planning in the Medical Sciences*, 39 SOC. STUD. SCI. 171, 198 (2009); Sergio Sismondo, *Ghost Management: How Much of the Medical Literature Is Shaped Behind the Scenes by the Pharmaceutical Industry?*, 4 PLOS

data on off-label use on an annual basis would also mitigate many of the perverse incentives to engage in the type of “loopholing” behavior discussed above.<sup>116</sup>

To be sure, annual reporting of off-label uses would not be without its own administrative costs. But these costs should not be overstated, particularly in light of the resources manufacturers already devote to off-label research and sales. The costs imposed by our proposed reporting requirement, therefore, are not search costs—that is, the manufacturer need provide only information that is already within its knowledge or that would be easily ascertainable. Instead, the costs are simply those of providing this information to a different audience: regulators, rather than potential customers.

In the spirit of the regulations we propose and in recognition of the potentially imperfect information available to manufacturers, the FDA could grant the manufacturers the kind of reporting flexibility that is apparent in other areas of FDA regulation.<sup>117</sup> The FDA could require manufacturers to use reasonable diligence to become informed and to report what they know. Finally, because manufacturers already do report to the FDA at regular intervals, including on an annual basis,<sup>118</sup> compliance with our proposal is highly unlikely to impose unreasonable or excessive costs on these businesses. Our proposal would thus avoid the perverse incentives toward antitransparency that currently prevail in manufacturers’ off-label practices and would impose few incremental costs on manufacturers.

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MEDICINE 1429, 1433 (2007); see Sergio Sismondo, *Key Opinion Leaders, the Corruption of Medical Knowledge, and the Sunshine Act*, 41 J. L. MED. & ETHICS 1, 27 (2013).

116. See Kesselheim, *supra* note 54, at 228 (discussing manufacturers’ use of improper off-label promotions). Annual reports could also require disclosure of a pharmaceutical company’s sponsorship of research and publications.

117. Cf. U.S. DEP’T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: POSTMARKETING ADVERSE EVENT REPORTING FOR NONPRESCRIPTION HUMAN DRUG PRODUCTS MARKETED WITHOUT AN APPROVED APPLICATION 5, 7 (2009), available at <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm171672.pdf> (discussing manufacturers’ obligation to disclose adverse events within fifteen days and emphasizing that, given the urgency of adverse events and the limited timeframe to file a report, a manufacturer’s efforts to provide adequate information need only be “reasonable”). A similar “reasonableness” standard would be appropriate here, and, as discussed above, such a standard would have clear precedents in FDA regulations.

118. See, e.g., U.S. DEP’T OF HEALTH & HUMAN SERVS., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CMC POSTAPPROVAL MANUFACTURING CHANGES REPORTABLE IN ANNUAL REPORTS 1–5 (2014) (discussing manufacturers’ annual-reporting requirements under other FDA regulations).

2. *Enhanced Reporting of Adverse Events.* The second element of our proposal to improve reporting calls for the reporting of diagnostic codes in AERS. Here, we suggest two straightforward changes to FDA policy in this area: allowing physicians to include diagnostic codes in their reporting of adverse events and imposing a duty of inquiry on manufacturers to ascertain the diagnostic codes of prescriptions in their reports. Data on patient diagnostic codes is particularly valuable because it can be used in data-mining strategies on large data sets to detect and analyze associations between off-label uses, diagnostic codes, and adverse events.<sup>119</sup> In 2011, the FDA received a total of 874,116 reports of adverse events.<sup>120</sup>

Under the current AERS regime, physicians do not report diagnostic codes of adverse events—even if they would be inclined to do so.<sup>121</sup> The reality, however, is that patients who experience adverse drug events usually have diagnostic codes associated with their indication for taking the drug (as well as for their comorbidities and the adverse event itself).<sup>122</sup> Similarly, in the vaccination context, researchers have demonstrated the effectiveness of including diagnostic codes in post-vaccination adverse events, even though such reporting entails the additional burden of following up with patients for a period following vaccination.<sup>123</sup> Physicians' use of diagnostic codes in reporting adverse events is neither universal nor perfect, but it ought to be an option available to doctors who do report adverse events to the FDA—particularly since many of them already

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119. Abbott, *supra* note 4, at 239.

120. *FDA Adverse Events Reporting System (FAERS): Reports Received and Reports Entered into FAERS by Year*, U.S. FOOD & DRUG ADMIN, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm> (last updated Aug. 6, 2013).

121. See Paul Hougland, Jonathan Nebeker, Steve Pickard, Mark Van Tuinen, Carol Masheter, Susan Elder, Scott Williams & Wu Xu, *Using ICD-9-CM Codes in Hospital Claims Data to Detect Adverse Events in Patient Safety Surveillance*, ADVANCES IN PATIENT SAFETY: NEW DIRECTIONS AND ALTERNATIVE APPROACHES 12–15 (2008), available at [http://www.ncbi.nlm.nih.gov/books/NBK43647/pdf/advances-hougland\\_26.pdf](http://www.ncbi.nlm.nih.gov/books/NBK43647/pdf/advances-hougland_26.pdf).

122. See *id.* at 2 (“Virtually all inpatient discharges are assigned International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes.”). As Paul Hougland and his colleagues have proposed, “[i]n the case of an adverse drug event (ADE), a diagnosis code would be used to indicate the patient’s general diagnosis . . . while the E-code would indicate the drug class thought responsible for these symptoms.” *Id.*

123. See ROSS LAZARUS, HARVARD PILGRIM HEALTH CARE, INC., ELECTRONIC SUPPORT SYSTEM FOR PUBLIC HEALTH – VACCINE ADVERSE EVENT REPORTING SYSTEM (2010), <http://healthit.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system/activity/2010> (last visited Nov. 5, 2014).

document these diagnostic codes for other purposes. Thus, under our proposal, physicians would have the ability to provide diagnostic codes in reporting adverse events, although they would not be required to do so. Requiring physicians to report diagnostic codes might burden physicians and discourage them from voluntarily submitting adverse events.

Manufacturers, in contrast, would have a duty of reasonable inquiry to determine the diagnostic code for the original prescription that gave rise to the adverse event. This requirement would impose minimal incremental burdens on manufacturers for at least three reasons. First, as discussed above, physicians often document the diagnostic codes of adverse events and also often notify manufacturers of the event; under our proposal, manufacturers could simply request that physicians relay the information that may well be in their possession already. Second, the FDA already requires manufacturers to provide a basic diagnosis, or something close to it, in reporting the adverse event. Under FDA regulations, “a serious adverse event should, at a minimum, be described in terms of signs (including abnormal laboratory findings), symptoms, or disease diagnosis for purposes of reporting.”<sup>124</sup> Indeed, the FDA “encourage[s], as appropriate, attachment of the following: (1) hospital discharge summaries, (2) autopsy reports, (3) relevant laboratory data, and (4) other critical clinical data” in manufacturers’ adverse event reports.<sup>125</sup> Finally, a duty of reasonable inquiry to determine the diagnostic code is consistent with manufacturers’ general obligations to investigate the facts of adverse events, which require manufacturers to follow up with medical personnel and victims to ascertain details that may not have been available at the time the incident was first reported.<sup>126</sup> Manufacturers would not be punished if physicians or hospitals refused to provide the diagnostic information, but they would have to maintain a system to ask the question (and to record and report the answer). Thus, by voluntarily collecting diagnostic codes from doctors and imposing a duty of inquiry on manufacturers, the FDA would gain a powerful tool in

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124. U.S. DEP’T OF HEALTH & HUMAN SERVS., *supra* note 117, at 6.

125. *Id.*

126. *See, e.g., id.* at 8 (explaining that “[i]f a report received by the responsible person refers to groups of unknown size, such as ‘some’ or ‘a few’ college students [who] got anaphylaxis, the responsible person should follow up to find out the number and then submit a separate report to FDA for each identifiable patient”).

gathering information regarding off-label drug use while imposing very few additional costs on physicians and manufacturers.

3. *Medicare/Medicaid Reimbursement Requests.* With the third element of our enhanced reporting proposal, we join other scholars in calling for the inclusion of diagnostic codes in all Medicare/Medicaid reimbursement requests. Currently, CMS requires diagnostic codes only under Medicare Part B.<sup>127</sup> As Jennifer Herbst has explained, the current Medicare/Medicaid system lacks a “single database within the federal healthcare system in which a patient’s outpatient prescription drug use can be cross-referenced with his medical diagnoses.”<sup>128</sup> This results in a suboptimal use of finite healthcare resources, as CMS pays for prescriptions not approved under the statutory language of Medicare Part D and Medicaid,<sup>129</sup> as well as in a lost opportunity to seize informational advantages and to fulfill the Obama administration’s goal of improving the storage of electronic medical records.<sup>130</sup> One solution, which Professor Herbst has persuasively put forth and which we support, is to “[m]ake patient diagnosis codes a necessary condition for payment of outpatient prescription drugs by

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127. CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE BENEFIT POLICY MANUAL, ch. 15, § 50.4.1, <http://www.cms.hhs.gov/Manuals/downloads/bp102c15.pdf> (last visited Nov. 5, 2014) (“Use of the drug or biological must be safe and effective and otherwise reasonable and necessary. . . . Drugs or biologicals approved for marketing by the Food and Drug Administration (FDA) are considered safe and effective for purposes of this requirement when used for indications specified on the labeling.”); CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE CLAIMS PROCESSING MANUAL, ch. 3, § 20, <http://www.cms.hhs.gov/manuals/downloads/clm104c07.pdf> (last visited Nov. 5, 2014); CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE CLAIMS PROCESSING MANUAL, ch. 17, § 80.1.3, <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c17.pdf> (last visited Nov. 5, 2014) (“A cancer diagnosis code must be reported when billing for [oral cancer drugs using] these HCPCS [Healthcare Common Procedure Coding System] codes. If there is no cancer diagnosis the claim is denied.”).

128. Jennifer L. Herbst, *How Medicare Part D, Medicaid, Electronic Prescribing and ICD-10 Could Improve Public Health (But Only If CMS Lets Them)*, 24 HEALTH MATRIX 209, 217 (2014).

129. Professor Herbst, for example, supports this finding by quoting a recent HHS report’s finding that “50 percent of Medicare Part D claims [reviewed] were erroneous because the claimed drugs were not provided for medically accepted indications.” *Id.* at 218 (quoting U.S. DEP’T HEALTH & HUMAN SERVS., OFFICE OF INSPECTOR GEN., ENSURING THAT MEDICARE PART D REIMBURSEMENT IS LIMITED TO DRUGS PROVIDED FOR MEDICALLY ACCEPTED INDICATIONS 6 (2011)).

130. Under the Health Information Technology for Economic and Clinical Health (HITECH) Act, passed as a part of the American Recovery and Reinvestment Act of 2009, healthcare professionals receive subsidies for transitioning to electronic medical records. *See* American Recovery and Reinvestment Act of 2009, Pub. L. 111-5, 123 Stat. 115 (codified at 42 U.S.C. §§ 300jj-11–300jj-51, §§ 17901–17940 (2012)).

Medicare Part D and Medicaid.”<sup>131</sup> For our purposes, the key benefit of this requirement would be an informational one: with this single step, we would gain the ability to link off-label Medicare/Medicaid prescriptions to those in other areas and thus be able to provide a more complete picture of the evolving (and untested) use of certain drugs. This would result in a very robust dataset, as CMS covers about one hundred million U.S. residents.<sup>132</sup> Not only would this have the additional benefit of potentially saving CMS billions of dollars, but it would also have a substantial impact on the private-insurance market because many private payers follow CMS coverage and reimbursement policies.<sup>133</sup>

We diverge from other scholars, including Professor Herbst, in proposing that Medicare/Medicaid reimbursements should *mandate* diagnostic codes. Professor Herbst, for example, has stopped short of giving her proposal the teeth we recommend because, if healthcare professionals could be denied reimbursement for failing to provide diagnostic codes, they “may decide to tailor their diagnostic coding practices for payment (and thus, effective treatment) purposes rather than reflecting their patients’ actual diagnoses.”<sup>134</sup> Because this outcome, in Professor Herbst’s view, would likely result in fraudulent prescriptions and risk patient safety, we should continue reimbursing prescribers and physicians who fail to include diagnostic codes in their reimbursement requests.<sup>135</sup>

We disagree. First, we believe that the risks Professor Herbst identifies are overstated. Because Medicare/Medicaid patients make up such a substantial portion of certain healthcare markets, including the majority of many prescribers’ customer bases and the majority of users of certain drugs, we believe that the professionals in these markets are far more likely to comply with providing diagnostic

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131. Herbst, *supra* note 128, at 211.

132. CTRS. FOR MEDICARE & MEDICAID SERVS., <http://www.cms.gov> (last visited Nov. 5, 2014).

133. Demetrios L. Kouzoukas, Anna D. Kraus & Katherine Sauser, *From Research to Revenue: Coverage and Reimbursement for Life Sciences Products—Coverage and Reimbursement Recommendations from the MEDCAC*, BLOOMBERG LAW, <http://bna.com/from-research-to-revenue> (Aug. 24, 2011); *see also, e.g.*, ZACKS EQUITY RESEARCH, *Reimbursement Decision for BSX’ Alair*, ZACKS, (Mar. 20, 2012), <http://www.zacks.com/stock/news/71644/Reimbursement-Decision-for-BSX-Alair> (noting that a positive reimbursement decision from CMS is expected to encourage private insurers to provide reimbursement).

134. Herbst, *supra* note 128, at 218.

135. *Id.*

codes—and, by extension, to pressure manufacturers to seek approval for certain off-label uses. Second, because of the size and complexity of the Medicare and Medicaid regimes in general, we believe that the only means to ensure compliance is to deny reimbursements to those who fail to provide diagnostic codes. This approach, though harsh, is the traditional way of incentivizing compliance with Medicare/Medicaid policies,<sup>136</sup> and we see no reason why this requirement should be the exception. Finally, with respect to Professor Herbst's concern about physicians responding to this requirement by writing fraudulent prescriptions (to provide drugs to their patients while also protecting their own reimbursements), we believe that she overlooks the capacity of the Medicare/Medicaid fraud-prevention apparatus to combat such activities. Indeed, just as President Obama's healthcare policy places increasing emphasis on enhancing data collection, it imposes stricter punishments on physicians who engage in Medicare/Medicaid fraud through inappropriate billing—targeting and deterring doctors who embrace precisely the strategies that Professor Herbst identifies, however noble their motives may be.<sup>137</sup> Denying Medicare/Medicaid reimbursements for healthcare professionals' failure to include diagnostic codes in the context of off-label drug use, therefore, is unlikely to present the challenges Professor Herbst identifies and is instead a critical step in promoting compliance with this policy.

4. *Enhanced Reporting in Prescription of Certain FDA-Designated Drugs.* We suggest that the FDA can and should be able to create a subset of certain designated drugs for which all scripts must include diagnostic use. This suggestion reflects a simple and long-recognized reality of off-label drug use in the United States: it is heavily concentrated in the uses of certain drugs, for which there is often little or no evidence supporting its effectiveness. For example, the off-label use of antidepressant drugs such as promethazine, clonazepam, and Seroquel all exceed 75 percent of their total use;<sup>138</sup> likewise, the National Comprehensive Cancer Network (NCCN)

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136. See, e.g., 42 C.F.R. § 413.20(e) (2014) (authorizing a Medicare intermediary to suspend reimbursement payments to a provider that fails to maintain adequate medical records, as defined by 42 C.F.R. § 413.20(d) (2014)).

137. See, e.g., U.S. DEP'T OF HEALTH & HUMAN SERVS. & U.S. DEP'T OF JUSTICE, *The Affordable Care Act and Fighting Fraud*, STOP MEDICARE FRAUD, <http://www.stopmedicarefraud.gov/aboutfraud/aca-fraud/index.html> (last visited Nov. 5, 2014).

138. Walton et al., *supra* note 103, at 1447.

estimates that 50 to 75 percent of all anticancer therapy prescriptions are off-label.<sup>139</sup> In areas such as these, particularly where there have been numerous adverse events or other “red flags” of potential harm, the FDA should have the option—though not the obligation—to impose stricter requirements, such as the use of a diagnostic code at the prescription stage. This is something that a number of insurers and managed care organizations already require internally, but they have no obligation to share their data with the FDA.

The key benefit of this policy would be to give the FDA the tools it needs to more closely monitor extrapolated uses of drugs where they are likely to be prevalent and harmful; although this level of information for all prescriptions may be unnecessary, it is important for the subset of drugs that have been of greatest concern for researchers, health professionals, and regulators. Further, to the extent that this designation would impose new costs on manufacturers of certain drugs, we expect that these manufacturers would either bear this cost or seek FDA approval for the use; we do not, in other words, anticipate that these prescriptions would universally halt in a manner that would be harmful to patients.

We emphasize that the data underlying such designations (such as the percentage of off-label use for certain drugs and the number of adverse events) is already well developed in the medical literature for a number of drugs, and that the FDA could likely work from existing information in choosing which drugs, if any, would be placed into this category.<sup>140</sup> This suggestion, therefore, would essentially allow the FDA to pick its battles, and do so without imposing substantial costs on manufacturers and healthcare professionals.

5. *Crowdsourcing Big-Data Analytics.* Together, the mechanisms we propose would produce a far more comprehensive picture of the scope of off-label use. The collected data would facilitate the FDA’s internal analyses, which in turn would improve agency determinations related to postmarket testing requirements and enforcement, discussed below.

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139. MCKINNEY ET AL., *supra* note 111, at 40.

140. See generally Laura Cuzzolin, Ada Zaccaron & Vassilios Fanos, *Unlicensed and Off-Label Uses of Drugs in Paediatrics: A Review of the Literature*, 17 *FUNDAMENTAL & CLINICAL PHARMACOLOGY* 125 (2003) (reviewing the literature concerning off-label uses of pediatric drugs).



The FDA should also leverage its resources by publishing the data it collects in a de-identified manner (that is, without patients' protected health information).<sup>141</sup> The dataset that would result from our proposed collection activities would have substantial value to a range of stakeholders. Government agencies, such as the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health, and the National Science Foundation, study off-label use and could use the data collected by the FDA to improve evidence-based regulations. This would also be the case with nonprofit organizations, such as the National Comprehensive Cancer Network (NCCN). CMS and private insurers would utilize the data to make coverage and formulary determinations. Academics would use the data for health-services research. Pharmaceutical companies would have the option to do the same to limit their tort liability, and they could use the data for new drug development. More ambitiously, to achieve vigorous participation, new incentives could be created for private parties to supplement the FDA's activities in this area.<sup>142</sup>

### *B. Improved Testing*

The second element of our proposal is to substantially expand the FDA's use of postmarket testing of off-label drug use. As the most basic method to enhance testing of off-label drug use, the FDA should more aggressively exercise the authority Congress granted it in 2007 to require more postmarket testing of off-label drug use, and to demand that manufacturers comply with the FDA's requests for such testing. Our primary proposal for improved reporting buttresses this recommendation: if the FDA had better information regarding off-label use, as we suggest it should, it would be in a far better position to identify the drugs in need of postmarket testing and far more likely to utilize PMRs effectively.

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141. As Professor Ryan Abbott has previously explained:

The public does not have unrestricted access to the FDA's data, but the FDA does provide the number of reports it has received for products over the past decade, and persons familiar with relational database creation can extract raw data from individual case safety reports. Also, the public can obtain individual case safety reports from FAERS through a Freedom of Information ("FOI") request to the FDA. Finally, the FDA publishes quarterly reports on potential serious side effects identified by FAERS and summarizes information about ongoing and completed postmarket safety evaluations of adverse experience reports.

Abbott, *supra* note 4, at 240 (citations omitted).

142. *See generally id.* (reviewing existing incentives and proposing an administrative bounty system to incentivize third parties to submit information to the FDA).

The FDA's decision to require postmarketing testing should be guided by a weighing of the following factors:<sup>143</sup>

1. *Frequency of off-label use.* Here, we suggest that drugs whose off-label use represents a substantial percentage—perhaps even a majority—of their overall use should attract the attention of regulators as likely candidates for postmarket testing.<sup>144</sup>

2. *Proximity of off-label use to approved use.* Here, we recommend a model that looks beyond the frequency of off-label use to consider how *different* those off-label uses are from the approved use. Thus, a high frequency of very similar—though off-label—uses may be less likely to trigger a requirement of postmarket testing than a low frequency of very different uses. Put another way, an off-label use whose extrapolation is along a continuous variable already relevant to the drug's approval (such as age or weight), and small in magnitude, should be less likely to trigger scrutiny than a use that introduces an altogether new variable (such as an off-label treatment of overactive bladders when the drug is approved for treatment of wrinkles and aging<sup>145</sup>). The logic of including this variable is related to our metapoint regarding extrapolation: we should have more confidence in the safety of modest (even if frequent) extrapolations than dramatic (even if infrequent) ones.

3. *Frequency of adverse events associated with off-label use.* This variable is relatively straightforward: a high frequency of adverse events should increase the appropriateness of postmarket testing.

4. *Difference between severity of adverse events associated with off-label use and severity of condition if untreated by off-label use.* Beyond the frequency of the adverse events, we propose a model that would weigh adverse events according to their severity. Thus, a handful of extremely severe adverse events (such as death) may be

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143. Consistent with our approach, regulators and commentators have discussed and applied a variety of risk-benefit principles to new drug approval. *See generally, e.g.*, Louis P. Garrison, Jr., Adrian Towse & Brian W. Bresnahan, *Assessing a Structured, Quantitative Health Outcomes Approach to Drug Risk-Benefit Analysis*, 26 HEALTH AFF. 684 (2007) (discussing the current risk-benefit framework for new drug approval and proposing an alternative structured framework).

144. Of course, as we discuss under variable 2, certain drugs have very frequent off-label use simply because that use is not so “off-label”—that is, the off-label use differs only very slightly from the approved use (for example, use by individuals just outside the approved age range, or use at dosages slightly outside the approved range). We do not, therefore, suggest that *all* drugs with heavy off-label use should automatically be subject to extensive postmarket testing; rather, by incorporating variable 2 into the analysis, we suspect that many drugs in this category would not require postmarket testing because their off-label use is so similar to the approved use.

145. *See* Feeley & Milford, *supra* note 112.

more likely to result in postmarket testing than a large number of less severe—yet still reportable—adverse events (such as mild headaches). Yet, as the title of this variable suggests, merely looking at the severity of adverse events cannot be sufficient. Instead, we must compare the severity of what could go wrong with the harm from not using the drug for this off-label purpose at all. In essence, this requires an evaluation of the potential upside of the use in comparison with the potential downside.<sup>146</sup> For example, using a medication that may relieve acne but has also resulted in some serious birth defects would be very likely to trigger a requirement of postmarket testing—here, the benefit of off-label use is relatively low whereas the cost may be extremely high. By contrast, using a drug that may cause heart attacks but has the potential to cure a fatal disease would be *less* likely to trigger testing requirements—here, the cost of not using the drug for this off-label purpose (death) is much greater than the cost of the harms that may result from doing so (serious potential side effects). The potential downside from the use is small because the patient was already expecting a poor outcome.

5. *Difference in sample size between approved use and off-label use.* Postmarket testing is more appropriate where the off-label use represents an extrapolation into the “hump” of the distribution versus into the “tail.” Postmarket testing is more likely to produce reliable results—and is thus more appropriate—where the population size of off-label users is sufficiently large. When extrapolating into the tail of relatively infrequent use, regulators without the possibility of credible testing will at times need to make the approval decision on the basis of other factors—such as proximity and the relative upside of the use—without the benefit of additional evidence.<sup>147</sup>

By formally considering these variables, and perhaps others, the FDA would have a more systematic and effective means of evaluating

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146. For a discussion comparing the expected upside and downside and exploring “asymmetric payoffs” and strategies to minimize downside risks while increasing upside risks, see NASSIM NICHOLAS TALEB, *ANTIFRAGILE: THINGS THAT GAIN FROM DISORDER* 157–67 (2012).

147. Note that this variable is distinct from the frequency of off-label use (variable 1). Here, our concern is not with how often people *actually* use a given drug off-label, but rather how large the group of *potential* off-label users might be. Whereas variable 1 expresses a sensitivity to the scale of off-label use (and thus to the scale of any potential harm from it), variable 5 instead focuses on the feasibility of studying off-label use as compared to approved use of a drug.

whether postmarket testing is necessary.<sup>148</sup> The results of applying these variables could be surprising: for example, the widespread use of a headache drug to cure a minor toe fungus where such use may result in stomach pains may be more likely to trigger the requirement of postmarket testing than the use of a similar headache drug to cure a terminal illness where this use may result in heart attacks. But we believe this holistic, multifactor analysis is necessary to optimize extrapolation of approved drugs, protect patients, and avoid sinking unnecessary costs into studies that are unlikely to meaningfully improve patient care. This framework is but one illustration of the kind of analysis that the FDA should adopt in evaluating the appropriateness of postmarket testing.

### *C. Improved Enforcement*

As the final component of our proposal, we call for a tiered labeling system to influence off-label prescribing and to enhance the FDA's ability to influence physicians' prescribing practices. This framework would allow the FDA to draw finer distinctions among various drug uses, and it would provide the agency both the regulatory teeth and the flexibility it presently lacks. A critical benefit to these mechanisms is that, once implemented, they would primarily rely on third parties and market forces for enforcement, and therefore require minimal agency resources.

Under the model we describe below, unapproved and potentially harmful drug uses could be grouped into categories that vary in the costs and liabilities they impose on prescribers and manufacturers: (1) red-box uses, (2) black-box uses, and (3) gray-box uses. The agency could retain unboxed warnings and precautions, and continue its practice of simply not listing off-label uses where there is inadequate information to support a warning. A new category of conditional off-label use would allow sponsors actively complying with PMRs and PMCs to promote the study to healthcare providers. REMS and ETASU could apply to a drug in any category. Table 1 summarizes these categories and their consequences for physicians, pharmacists, and patients:

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148. Though we have stopped short of supplying a formula that incorporates these variables, we can imagine several possible iterations (for example, where  $T$  represents the appropriateness of testing,  $T = a*b + c*d + e$ ).

Table 1. Enforcement Mechanisms by FDA Designation

| FDA Designation   |                                 | Physician/<br>Pharmacist<br>Liability | Required<br>Diagnostic<br>Codes | Promotion<br>Bar | Denial of<br>Medicare/<br>Medicaid<br>Reimbursement | Heightened<br>Malpractice<br>Liability |
|---|---------------------------------|---------------------------------------|---------------------------------|------------------|---|--|
| Red-Box<br>Uses   | R E<br>E T<br>M A<br>S S<br>& U | ✓                                     | ✓                               | ✓                | Black   | Black                                  |
| Black-Box<br>Uses   |                                 |                                       | ✓                               | ✓                |   |  |
| Gray-Box<br>Uses  |                                 |                                       | ✓                               | ✓                |   |  |
| Unboxed<br>Warning  |                                 |                                       |                                 | ✓                | Gray  | Gray                                   |
| No Warning  |                                 |                                       |                                 | ✓                | Gray  | Gray                                   |
| Conditional<br>Off-Label  |                                 |                                       |                                 |                  | White   | White                                  |
| On-Label  |                                 |                                       |                                 |                  | White   | White                                  |
| Check marks indicate the presence of an enforcement mechanism. Shading indicates the extent to which the mechanism is present: black (fully present), gray (somewhat present), and white (not present). The REMS & ETASU column indicates that FDA use designations could be combined with REMS and ETASU requirements. |                                 |                                       |                                 |                  |   |  |

As Table 1 suggests, a drug use that falls into one of the stronger labeling categories is subject not only to its own unique enforcement mechanism, but also to downstream enforcement mechanisms associated with less stringent labeling categories. For example, both red-box and gray-box warnings require a diagnostic code to be associated with a prescription. With regard to malpractice liability, any off-label use is associated with enhanced liability to the extent it differs from the standard of care. However, stricter FDA warnings would influence the standard of care both by directly impacting the way doctors prescribe, and by serving as evidence of the standard of care in malpractice suits. In this way, violating a red-box warning would be stronger evidence of malpractice than prescribing off-label in the absence of any warning.<sup>149</sup> Assignment to labeling categories would be facilitated by the improved reporting mechanisms discussed previously.

As the most severe enforcement category, which we might consider the “nuclear” option, we propose a new red-box warning that would be reserved for the most dangerous and most problematic instances of off-label drug use. For the rare uses that would fall within this category, physicians and pharmacists would face liability for their

149. For further background on the increased risk of malpractice liability in the context of off-label drug use, including for drugs with black-box warnings, see Judith G. Edersheim & Theodore A. Stern, *Liability Associated with Prescribing Medications*, 11 PRIMARY CARE COMPANION J. CLINICAL PSYCHIATRY 115, 117–18 (2009).

roles in making and filling such prescriptions.<sup>150</sup> The simplest liability mechanism could be a statement to the effect that the FDA considers violating a red-box warning conclusive evidence of malpractice and grounds for discipline by a state board. This would not guarantee practitioner liability, as it would depend on state courts and medical boards for enforcement, but it would avoid the need for the agency to be responsible for enforcement at the provider level, something it does not currently do. State courts and medical boards would have to be willing to accept the FDA's authority in this area, and state legislatures would have to acquiesce to and not obstruct the FDA's augmented role. In today's political environment, it is easy to imagine a state legislature passing a law to the effect that providers cannot be held liable in state tort suits for violating red-box warnings. This possibility is not necessarily fatal to our proposal, as having some states challenge red-box warnings would essentially create a randomized trial to measure the efficacy of the red-box system. In any case, regardless of the extent to which provider liability is enforced by third parties, an FDA statement to the effect that a red-box violation is malpractice and grounds for discipline is likely to have a very strong effect on prescribing practices. More ambitiously, a statutory amendment might provide for direct civil liability to the agency. Whatever the nature of red-box liability, this category of warnings would be designed to completely prohibit particular off-label uses. However, in the event that an individual patient had an unusual and compelling need that might justify an off-label use in violation of a red-box warning, the FDA could consider exceptions on a patient-by-patient basis with the agency's approval (similar to the compassionate use program).<sup>151</sup>

A black-box warning, by contrast, would represent an intermediate level of enforcement. In this category, physicians would remain free to make such prescriptions, and pharmacists would face no special liability for filling them. However, as with black-box warnings now, the disclosure would be prominent, and providers would be discouraged from violating black-box warnings due to

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150. An example might be the use of thalidomide in a pregnant patient. Margaret Hamburg, *50 Years After Thalidomide: Why Regulation Matters*, FDA VOICE (Feb. 7, 2012), <http://blogs.fda.gov/fdavoices/index.php/2012/02/50-years-after-thalidomide-why-regulation-matters>.

151. See *Understanding Expanded Access/Compassionate Use*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForPatients/Other/ExpandedAccess/ucm20041768.htm> (last updated Oct. 23, 2014) (discussing the FDA's compassionate use program).

malpractice liability. For uses that are not concerning enough to prohibit outright with red-box warnings but too concerning to allow providers to prescribe routinely, the FDA could combine black-box warnings with ETASU requirements. As a novel ETASU mechanism, certain uses might require written informed consent from patients for the off-label use.<sup>152</sup> To the extent that the off-label use in question is concerning, requiring informed consent would reduce the prevalence of that use because obtaining written informed consent from patients is somewhat burdensome on physicians. It would also improve patient engagement and education.

Gray-box warnings would be intended to eliminate insurance coverage for particular off-label uses by stating that there is evidence that the risks are likely to exceed the benefits for a specific off-label use. Gray-box warnings should prevent Medicare/Medicaid reimbursement. While CMS does not generally reimburse for off-label use, it may as a result of private compendia or its internal analyses. Gray-box warnings, however, should presumptively preclude CMS reimbursement, unless CMS makes a deliberate decision to the contrary.<sup>153</sup> Gray-box warnings would allow the FDA to disseminate its internal analyses, along with analyses it collects from elsewhere (including from CMS, the European Medicines Agency, and academic publications) and validates. This system would also promote greater interagency collaboration. A gray-box warning is also likely to have a strong impact on private-insurance-reimbursement decisions, as it works to control healthcare costs, and because private-insurance reimbursement often tracks CMS reimbursement.

For any drug with any category of boxed warning, we propose that physicians should be required to report diagnostic codes before a prescription can be filled. Pharmacies would then be responsible for submitting this data to the FDA. For drugs that are concerning enough to warrant an off-label boxed warning, it is important that

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152. See *REMS and Opioid Analgesics Webinar Outline*, U.S. FOOD & DRUG ADMIN. 13, <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM163668.pdf> (last visited Nov. 5, 2014). Under the FDA's ETASU requirements for this class of drugs, the prescribing physician must monitor the patient every six months, and the patient must be enrolled in a registry. *Id.*

153. Compendia have been criticized as lacking in consistency, quality, transparency, and timeliness. Tillman et al., *supra* note 65, at 349. Reimbursement based on compendia can be required by statute, so this particular mechanism may require statutory amendment. R. Dresser & J. Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J. L. MED. & ETHICS 476, 480 (2009).

accurate data be available on the scope of the off-label use. For uses that do not warrant a boxed warning, we would retain the existing system for unboxed warnings and precautions.<sup>154</sup> Of course, not all off-label uses are associated with a warning, so the vast majority of off-label uses would not be listed on the label or associated with any kind of warning (“off-label” in Table 1).

There is a risk with boxed warnings, particularly with red-box warnings, that the FDA will prevent potentially beneficial uses. Therefore, these warnings should be implemented sparingly. The risk of chilling beneficial uses is significantly less with the use of unboxed warnings. The warnings would not be entirely toothless: the disclosure requirements would impose additional costs on manufacturers and prescribers, and heightened malpractice liability would be associated with unapproved use of the drug. But enforcement against off-label uses of drugs in this category would be significantly less stringent than in boxed categories. Unboxed warnings would thus make sense as only one of several effective tools in the FDA’s toolbox. This spectrum of regulatory options would allow the FDA to better distinguish between high-risk uses and likely harmless ones.

Finally, our enforcement system could be used to improve sponsor compliance with agreed-upon postmarket studies using a package of the proverbial sticks and carrots. Namely, sponsors actively completing PMRs and PMCs would be permitted to inform healthcare providers about their studies as part of the “conditional off-label” designation.<sup>155</sup> This designation would remove the promotion bar for discussing off-label uses within the context of the clinical trial, and it would be a positive incentive for sponsors to conduct trials. In the event a sponsor failed to meet milestones for its PMRs and PMCs, such failures would automatically trigger a gray-box warning, followed eventually by a black-box warning. This system would provide a stronger series of incentives for manufacturers to

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154. U.S. DEP’T OF HEALTH & HUMAN SERVS. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, AND BOXED WARNING SECTIONS OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS – CONTENT AND FORMAT (2011), available at <http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf>.

155. This is more liberal than the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, which permitted pharmaceutical companies to advertise that they were conducting a clinical trial when it was for the purposes of a new-use approval. *See id.* § 401, 111 Stat. at 2357–58. That regulation has expired. *See id.*, 111 Stat. at 2364.



complete agreed-upon trials, and has the advantage of taking effect without a significant additional expenditure of agency resources or the need to overcome bureaucratic inertia or make a politically contentious determination. However, the agency would have the option to postpone or prevent the automatic implementation of a boxed warning for good cause.

### III. ILLUSTRATIVE CASE STUDIES: SEROQUEL AND LAP-BAND

#### A. *The Making of an All-Purpose Psychiatric Drug*

Psychosis is a loss of contact with reality.<sup>156</sup> Symptoms of psychosis include delusions (false beliefs not amenable to change in light of conflicting evidence), hallucinations (perception-like experiences that occur without an external stimulus), and disorganized thinking.<sup>157</sup> Psychotic patients are at risk for agitation, aggression, and impulsivity which can make them a danger to themselves and others.<sup>158</sup> Psychosis can occur as the result of underlying mental illness—for example, as a result of schizophrenia. Schizophrenia is a psychiatric disorder involving chronic or recurrent psychosis,<sup>159</sup> and is one of the top twenty causes of disability worldwide.<sup>160</sup> Psychosis may also be caused by mental illnesses such as bipolar mania or depression with psychotic features.<sup>161</sup> It is also common in patients with dementia or delirium; up to 40 percent of patients with Alzheimer's disease have psychotic symptoms.<sup>162</sup> In addition, psychosis can occur as a result of general medical conditions or a substance-use disorder.<sup>163</sup> Psychosis is relatively common—it

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156. AM. PSYCHIATRIC ASS'N, THE DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS § 309.81 (4th ed. 1994).

157. *Id.*

158. *Id.*

159. Michael D. Jibson, *Overview of Psychosis*, UPTODATE, [http://www.uptodate.com/contents/overview-of-psychosis?source=search\\_result&search=psychosis&selectedTitle=1%7E150](http://www.uptodate.com/contents/overview-of-psychosis?source=search_result&search=psychosis&selectedTitle=1%7E150) (last updated Nov. 1, 2013).

160. T. Vos et al., *Years Lived with Disability (YLDs) for 1160 Sequelae of 289 Diseases and Injuries 1990–2010: A Systematic Analysis for the Global Burden of Disease Study 2010*, 380 LANCET 2163, 2196 (2012).

161. AM. PSYCHIATRIC ASS'N, *supra* note 156, at 87–88.

162. *See* Jibson, *supra* note 159.

163. AM. PSYCHIATRIC ASS'N, *supra* note 156, at 87–88.

affects more than 3 percent of the population at some point in their lives.<sup>164</sup>

The primary treatment for psychosis and schizophrenia is antipsychotic medications.<sup>165</sup> The first generation of these drugs, “typical antipsychotics,” was discovered starting in the 1950s.<sup>166</sup> These drugs are effective, but they also cause significant side effects.<sup>167</sup> First-generation antipsychotics can cause permanent abnormal body movements, including tremors and Parkinson’s disease-type movements, as well as body rigidity and neuroleptic malignant syndrome, a rare but potentially fatal side effect.<sup>168</sup> They also cause a host of other problems, ranging from sexual dysfunction, to excessive sedation, to endocrine disorders.<sup>169</sup> These problems are prevalent and severe enough that patient noncompliance with directions to use typical antipsychotics is common.<sup>170</sup> The second generation of antipsychotic drugs, “atypical antipsychotics,” was thought to be far safer.<sup>171</sup> The first atypical antipsychotic agent, Clozapine, was marketed heavily on the basis of an improved side-effect profile, as were the other atypical antipsychotic agents that followed.<sup>172</sup> Aggressive marketing continued even as evidence emerged that contradicted those safety claims.<sup>173</sup> For example, a 2005 study in the

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164. See Jonna Perälä et al., *Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population*, 64 ARCHIVES GEN. PSYCHIATRY 19, 19 (2007).

165. See John M. Grohol, *Schizophrenia Treatment*, PSYCHCENTRAL, <http://psychcentral.com/disorders/sx31t.htm> (last updated Oct. 9, 2013).

166. See Michael D. Jibson, *First-Generation Antipsychotic Medications: Pharmacology, Administration, and Comparative Side Effects*, UPTODATE, <http://www.uptodate.com/contents/first-generation-antipsychotic-medications-pharmacology-administration-and-comparative-side-effects> (last updated Mar. 11, 2014); Michael D. Jibson, *Second-Generation Antipsychotic Medications: Pharmacology, Administration, and Comparative Side Effects*, UPTODATE, <http://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-comparative-side-effects> (last updated Apr. 30, 2014) (comparing first- and second-generation antipsychotics).

167. See sources cited *supra* note 166.

168. See sources cited *supra* note 166.

169. See PATRICK W. CORRIGAN ET AL., PRINCIPLES AND PRACTICE OF PSYCHIATRIC REHABILITATION: AN EMPIRICAL APPROACH 163, 167–68 (2008); John Muench & Ann M. Hammer, *Adverse Effects of Antipsychotic Medications*, 81 AM. FAM. PHYSICIAN 617, 619–21 (2010).

170. See Ghaseen Saba et al., *Patients’ Health Literacy in Psychotic Disorders*, 3 NEUROPSYCHIATRIC DISEASE & TREATMENT 511, 511 (2007).

171. See sources cited *supra* note 166.

172. See Herbert Y. Meltzer, *Clozapine: Balancing Safety with Superior Antipsychotic Efficacy*, CLINICAL SCHIZOPHRENIA & RELATED PSYCHOSES, Oct. 2012, at 134, 135–36.

173. See *id.*

*New England Journal of Medicine* showed that the increase in the risk of death for elderly patients taking atypical antipsychotic agents was on par with that associated with taking typical antipsychotic agents.<sup>174</sup> On the basis of a review of the existing evidence in 2008, the editors of the *Lancet* concluded that “the time has come to abandon the terms *first-generation* and *second-generation* antipsychotics, as they do not merit this distinction.”<sup>175</sup>

Seroquel (one of the brand names for the generic drug quetiapine fumarate) is a second-generation antipsychotic manufactured by AstraZeneca that was approved by the FDA in 1997.<sup>176</sup> It is now approved for the treatment of schizophrenia and mania-associated bipolar disorder, and Seroquel XR (the extended-release iteration of the drug) is approved for adjunct treatment of major depressive disorder (MDD).<sup>177</sup> Over its lifetime, Seroquel has been subject to sixty-one labeling revisions, efficacy-supplement additions, patient-population alterations, packaging changes, and indication modifications.<sup>178</sup> In 2009, a black-box warning was added to advise that elderly patients with dementia-related psychosis treated with Seroquel are at an increased risk of death, and that Seroquel increases the risk of suicide in young persons.<sup>179</sup> Those risks apply to

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174. Philip S. Wang, Sebastian Schneeweiss, Jerry Avorn, Michael A. Fischer, Helen Mogun, Daniel H. Solomon & M. Alan Brookhart, *Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications*, 353 NEW ENG. J. MED. 2335, 2335 (2005).

175. Peter Tyrer & Tim Kendall, *The Spurious Advance of Antipsychotic Drug Therapy*, 373 LANCET 4, 5 (2009) (emphasis added).

176. See U.S. FOOD & DRUG ADMIN., LABEL AND APPROVAL HISTORY, DRUGS@FDA: FDA APPROVED DRUG PRODUCTS, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails> (search for “SEROQUEL”; then follow “SEROQUEL”) (last visited Nov. 5, 2014) (“Original Approval . . . Date September 26, 1997”).

177. U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: SEROQUEL (QUETIAPINE FUMARATE) TABLETS (2013), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/020639s061lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020639s061lbl.pdf); U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: SEROQUEL XR (QUETIAPINE FUMARATE) TABLETS (2013), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022047s034lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022047s034lbl.pdf).

178. U.S. FOOD & DRUG ADMIN., *supra* note 176.

179. *Drug Safety Labeling Changes: Seroquel (quetiapine fumarate) Tablets August 2008*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm123259.htm> (last updated June 19, 2009) (“Warning: Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. . . . SEROQUEL is not approved for the treatment of patients with dementia-related psychosis.”).

the entire class of atypical antipsychotics.<sup>180</sup> Also in 2009, the FDA required AstraZeneca to implement a REMS for Seroquel, which required a medication guide and periodic assessments that included a survey of patients' understanding of the potential risks of Seroquel, including mortality in the elderly, hyperglycemia, hypercholesterolemia, and weight gain.<sup>181</sup> The REMS was "released" (discontinued) in November 2011.<sup>182</sup> However, the FDA continues to require the medication guide as part of the approved labeling for Seroquel.<sup>183</sup>

Off-label uses of Seroquel are common—and troubling. For example, the AHRQ found that "at one large acute-care psychiatric hospital, [Seroquel] was used extensively for off-label conditions, and in a variety of off-label doses."<sup>184</sup> Moreover, "only a quarter of patients had one of the diagnoses for which [Seroquel] is approved, and only a third received [Seroquel] in a standing dose regimen. Depression and substance-use disorders were found to be the most common associated diagnoses."<sup>185</sup> Other off-label uses are for sleep disorders, anxiety, autism, panic attacks, headaches, restlessness, nervousness, dementia, and agitation.<sup>186</sup> An investigation of Florida's Department of Juvenile Justice found that the agency bought twice as much Seroquel as Ibuprofen in 2007, "routinely [doling it] out for reasons that never were approved by federal regulators."<sup>187</sup> Military spending on Seroquel has increased "more than sevenfold" since 2001, as veterans' doctors frequently prescribe it for insomnia and

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180. *Id.*

181. *FDA Approves Once-Daily SEROQUEL XR Extended Release Tablets*, NEWS MED. (Dec. 4, 2009, 7:37 AM), <http://www.news-medical.net/news/20091204/FDA-approves-once-daily-SEROQUEL-XR-Extended-Release-Tablets.aspx>.

182. *Postmarket Drug Safety Information for Patients and Providers: Released REMS*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm393231.htm> (last updated Aug. 12, 2014).

183. U.S. FOOD & DRUG ADMIN., *RELEASE REMS REQUIREMENT 2* (Nov. 2011), [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2011/020639s0551tr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020639s0551tr.pdf).

184. Margaret Maglione et al., *Off-Label Use of Atypical Antipsychotics: An Update*, 43 *COMPARATIVE EFFECTIVENESS REVIEWS* 20 (2011), <http://www.ncbi.nlm.nih.gov/books/n/cer43/pdf/>.

185. *Id.*

186. *See id.* at 29–33 (listing treatment for a variety of conditions, some involving off-label uses of antipsychotics).

187. Michael LaForgia, *Huge Doses of Potent Antipsychotics Flow into State Jails for Troubled Kids*, PALM BEACH POST, May 24, 2011, at 1A.

post-traumatic stress disorder.<sup>188</sup> The Institute for Safe Medication Practices found that 47 percent of the adverse events from 2004 to 2010 occurred when the drug was being used off-label.<sup>189</sup> Off-label uses of Seroquel also occur in violation of its black-box warning. Elderly patients with dementia continue to receive Seroquel in significant numbers, despite the evidence of increased risk of death and the availability of alternate treatment options such as mood stabilizers.<sup>190</sup> As of 2010, a study found that it was still the case that almost “10% of prescription drug uses for dementia among elderly patients are for atypical antipsychotics.”<sup>191</sup>

The prevalence of Seroquel’s off-label uses should not be surprising, because AstraZeneca promoted the drug aggressively for such uses.<sup>192</sup> As Seroquel became increasingly profitable, AstraZeneca even engineered deliberately misleading promotions.<sup>193</sup> The company promoted the drug as better than generic without scientific evidence, and as weight-neutral despite knowing that Seroquel caused weight

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188. Matthew Perrone, *Deaths Raise Questions on Drug Given to Sleepless Vets*, NBC NEWS, Aug. 30, 2010, [http://www.nbcnews.com/id/38917668/ns/health-mental\\_health/t/deaths-raise-questions-drug-given-sleepless-vets/](http://www.nbcnews.com/id/38917668/ns/health-mental_health/t/deaths-raise-questions-drug-given-sleepless-vets/).

189. Jim Edwards, *How Seroquel, a Risky Antipsychotic, Became a “General Purpose” Mental Health Drug*, CBS MONEY WATCH (Mar. 27, 2011, 4:48 PM), <http://www.cbsnews.com/news/how-seroquel-a-risky-antipsychotic-became-a-general-purpose-mental-health-drug>.

190. Sudeep S. Gill et al., *Antipsychotic Drug Use and Mortality in Older Adults with Dementia*, 146 ANN. INTERN. MED. 775, 775 (2007).

191. Dorsey et al., *supra* note 98, at 101. In 2003, there were 590,000 drug uses in which atypical antipsychotics were used among individuals sixty-five years and older with dementia. *Id.* at 99. That number peaked in 2004 at 780,000 uses, then declined to 400,000 in 2008 (the last year examined in the study). *Id.* The study concluded that the black-box warning decreased use of the medication. *Id.* at 96. Still, the use of atypical antipsychotics for dementia continues. *Id.* The study also noted that the most recent figures on new atypical antipsychotic prescriptions, from December 2008, showed “there were 8000 new atypical drug uses each month among patients with dementia, despite the increased risk of death and limited evidence of their efficacy.” *Id.* at 101.

192. Edwards, *supra* note 189.

193. Duff Wilson, *For \$520 Million, AstraZeneca Settles Case over Marketing of a Drug*, N.Y. TIMES, Apr. 27, 2010, <http://www.nytimes.com/2010/04/28/business/28drug.html> (“AstraZeneca paid kickbacks to doctors as part of an illegal scheme to market drugs for unapproved uses,” Kathleen Sebelius, secretary of health and human services, said . . .”). Moreover,

From 2004 to 2008, the mean cost of typical antipsychotic prescription increased 8% from \$38 to \$41, while the cost of an atypical prescription increased by 43% from \$226 to \$323. In 2008, US \$0.06 billion was spent on typical agents and \$9.9 billion spent on atypical agents in the United States. Given these costs, we estimate that in 2008 \$6.0 billion was expended on off-label use of antipsychotic medications, of which \$5.4 billion was for uses with uncertain evidence.

Alexander et al., *supra* note 40, at 181.

gain.<sup>194</sup> Seroquel became a “general purpose psychiatric drug.”<sup>195</sup> AstraZeneca’s promotion campaign was enormously successful, and Seroquel earned \$4.87 billion for the company in 2009.<sup>196</sup> Although total AstraZeneca earnings stood at \$33 billion in 2010, Seroquel sales made up 40 percent of the company’s pretax profit.<sup>197</sup> The pretax profit margin on Seroquel sales exceeded 80 percent.<sup>198</sup>

Eventually, AstraZeneca was sued by the Department of Justice (DOJ) for promoting off-label uses.<sup>199</sup> The DOJ settled its case for \$520 million in 2009, noting, “the company recruited doctors to serve as authors of articles that were ghostwritten by medical literature companies . . . about studies the doctors in question did not conduct. AstraZeneca then used those studies and articles as the basis for promotional messages about unapproved uses of Seroquel.”<sup>200</sup> The company was also sued by numerous patients.<sup>201</sup> In 2010, AstraZeneca settled two-thirds of the lawsuits against them for a total of \$198 million.<sup>202</sup> However, perverse incentives are at work: the drug was so profitable that even after the FDA required the company to warn

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194. Jim Edwards, *E-Mail: AstraZeneca Knew in 1997 That Seroquel Caused Weight Gain*, CBS MONEY WATCH (Mar. 3, 2009, 2:40 PM), <http://www.cbsnews.com/news/e-mail-astrazeneca-knew-in-1997-that-seroquel-caused-weight-gain> (“AstraZeneca knew as far back as 1997 that Seroquel put patients at risk of weight gain, according to the company’s own internal memos. The documents also appear to show that some [AstraZeneca] executives developed strategies to ‘neutralize’ [the claim that] Seroquel caused weight gain or diabetes, even after the FDA asked the company to warn patients about Seroquel’s diabetes side effect.”); *see also* Jim Edwards, *The Dog Ate AstraZeneca’s Homework! Evidence on Misleading Drug Ad Disappears from Company’s Files*, CBS MONEY WATCH (July 10, 2010, 6:40 PM), <http://www.cbsnews.com/news/the-dog-ate-astrazenecas-homework-evidence-on-misleading-drug-ad-disappears-from-companys-files> (“AstraZeneca (AZN) says it has lost a crucial internal document that would explain how an ad for its antipsychotic Seroquel misleadingly claimed there was ‘no weight gain’ with the drug and described its ‘favorable weight profile.’”).

195. Edwards, *supra* note 189.

196. Jim Edwards, *AstraZeneca’s Marketing Strategy: Sue Us, Please!*, CBS MONEY WATCH (Aug. 5, 2010, 11:06 AM), <http://www.cbsnews.com/news/astrazenecas-marketing-strategy-sue-us-please>.

197. Jim Edwards, *How a Single Patent Expiry Could Wipe Out 40% of AstraZeneca’s Profits*, CBS MONEY WATCH (Feb. 7, 2011, 5:07 PM), <http://www.cbsnews.com/news/how-a-single-patent-expiry-could-wipe-out-40-of-astrazenecas-profits>.

198. *Id.*

199. U.S. DEP’T OF JUSTICE, *Pharmaceutical Giant AstraZeneca To Pay \$520 Million for Off-label Drug Marketing* (2010), <http://www.justice.gov/opa/pr/2010/April/10-civ-487.html>.

200. *Id.*

201. Edwards, *supra* note 196.

202. *Id.*

that Seroquel may cause diabetes<sup>203</sup> the company continued to use promotional materials without the warning.<sup>204</sup> Financially, it worked out that it was more profitable to continue with misleading advertisements and to settle civil claims than to provide accurate information to potential users.<sup>205</sup>

### *B. The Seroquel Dynamic Extrapolation Approach*

Seroquel can illustrate the advantages of our proposed framework. However, this Section is only intended to highlight key considerations and broad policy options; definitive determinations related to testing and labeling requirements would require a far more detailed evaluation.

The case of Seroquel raises two primary extrapolation-related issues: First, should Seroquel be used for unapproved conditions, and if so, which conditions? For example, should it be used for anxiety or dementia or post-traumatic stress disorder? Second, should Seroquel be used in different populations than those for which it was originally approved? In other words, should it be used in very young or very old populations, or in the pregnant-women population, none of which were examined in the original preapproval process? Other extrapolation issues include duration of use and substitution: Should Seroquel be prescribed for a longer time period than the duration of treatment evaluated in preapproval testing? Should it be used indefinitely when there is limited information available about long-term use? Can Seroquel XR safely be used in place of Seroquel?

To evaluate all of these extrapolation issues, our approach begins with data collection. For a new drug, this would include only preapproval clinical data, or data available from foreign countries if the drug has already been in use outside the United States. For a drug like Seroquel that has been in use for about fifteen years since its initial FDA approval, observational data will be available for each individual extrapolation. However, the data currently available to the agency is inferior to the data that would be available under the collection system we propose. Unfortunately, because the data we

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203. Letter from Michelle Safarik, Regulatory Review Officer, Div. of Drug Marketing, Adver., & Commc'ns, U.S. Food & Drug Admin. to James L. Gaskill, Dir., Promotional Regulatory Affairs, AstraZeneca LP (July 29, 2010), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM221315.pdf>.

204. *Id.*; Edwards, *supra* note 196.

205. Edwards, *supra* note 196.

advocate the FDA to collect is not available, it cannot be used here to demonstrate how it would affect downstream decisions related to testing and labeling. Our case study is restricted to the data currently available. Still, under the collection system we propose, regulators would have a far-clearer picture of Seroquel's off-label use. Because Seroquel has a boxed warning, under our framework physicians would be required to report the indication for which the drug is being prescribed.

With regard to postmarket studies, each extrapolation requires its own analysis. Our case-study analysis will focus on an off-label use that has been particularly concerning to regulators: using Seroquel for dementia-related psychosis in elderly patients. In fact, that off-label use is a combination of two distinct extrapolations, as the drug is being prescribed for an unapproved use (dementia) and in an unstudied population (geriatric patients). Combining multiple extrapolations has the potential to create safety problems that might not exist with either extrapolation in isolation. In the case of this combined extrapolation, the following factors would support an argument in favor of additional testing: a substantial percentage of Seroquel's overall use was off-label, as well as used off-label specifically for dementia and geriatric treatment; Seroquel's off-label use occurred, in part, across discrete conditions (schizophrenia versus dementia); adverse events were relatively frequent (for example, there was a greater than 5 percent incidence of weight gain) and severe (for example, the risk of death for Seroquel users rose to between 1.6 to 1.7 times the risk of death in placebo-treated patients); and, there is a large population of off-label users. Mitigating the need for postmarket testing would be the fact that Seroquel treats symptoms of dementia, which are serious, and that the off-label use here was in part along a continuous variable (age).

The factor-weighting analysis here supports requiring postmarket testing. This type of analysis would be an ongoing process for each extrapolation, so when data collection or surveillance reveals, for example, a higher incidence of off-label use for geriatric patients, that might alter the calculus enough to trigger the need for a postmarket study. A determination as to what type of study or methodology the FDA should mandate where analysis supports requiring postmarketing testing is beyond the scope of this analysis. In general, the FDA could require studies ranging from randomized clinical trials to prospective or retrospective cohort studies (in which a population is followed forward or backward in time). A randomized controlled



trial would produce the strongest results, but would need to be balanced against the reality that controlled trials are more resource intensive, and that it would be impracticable to require a controlled trial for every possible extrapolation.<sup>206</sup> Moreover, such trials may sometimes be unethical: given what is now known about the increased risk of death in elderly patients using Seroquel, it would be unethical to expose such patients to a controlled trial. Earlier in the drug's lifecycle, however, that risk was not yet clear: a trial may well have averted the ultimate harm done by the continued unchecked use of the drug in that population. Ultimately, the risk was established in a meta-analysis of seventeen placebo-controlled trials of atypical antipsychotic drugs.<sup>207</sup> Regardless of the nature of the postmarket testing, if the agency is going to permit continued use without warning, additional study is required.

With regard to labeling, should the FDA require ETASU or a red-box warning? In 2010, the AHRQ evaluated thirty-eight trials on dementia, six of which compared Seroquel to a placebo. The meta-analysis found a positive, significant difference between the atypical antipsychotics as a class and the placebo, though the effect was small in magnitude.<sup>208</sup> The pooled estimate of effect for Seroquel was not statistically significant.<sup>209</sup> This evidence suggests that Seroquel is not effective at treating symptoms associated with dementia in elderly patients. On the other hand, the AHRQ analysis found "high strength evidence from meta-analyses that the use of atypical antipsychotics is associated with an increased risk of death in elderly patients with dementia and agitation." In other words, there is no evidence of benefit, but strong evidence of an increased risk of death. On that basis, the FDA should issue a red-box warning for this off-label use.

Even under the best of circumstances, FDA analysis and decisionmaking will not be perfect. Where the risk-benefit analysis is not clear enough to support a red-box warning, a black- or gray-box warning will be more appropriate. Further, when the FDA implements a red-box warning, or withdraws a drug altogether, the agency should continue monitoring any available data. That may

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206. See Robert William Sanson-Fisher et al., *Limitations of the Randomized Controlled Trial in Evaluating Population-Based Health Interventions*, 30 AM. J. OF PREVENTIVE MED. 155, 156-58 (2007).

207. U.S. FOOD & DRUG ADMIN., *supra* note 176.

208. Maglione et al., *supra* note 184, at 117.

209. *Id.*

occur, for example, if the drug continues to be used in foreign countries.<sup>210</sup> In the event subsequent evidence alters the factors weighed by the agency to make labeling determinations, the FDA may need to revise its initial determination in light of an evolving evidence base.

### C. 1-800-GET-THIN!

The Lap-Band Adjustable Gastric Banding System (“Lap-Band”) is a medical device manufactured by Allergan to promote weight loss in obese patients. Obesity is determined by body mass index (BMI), which is calculated by dividing a patient’s weight (in kilograms) by the square of the patient’s height (in meters).<sup>211</sup> The Lap-Band “restrict[s] the size of the stomach to promote early satiety and appetite control leading to weight loss.”<sup>212</sup> Typically the device is placed via laparoscopic adjustable gastric banding (LAGB) surgery: “an inflatable gastric band connected to a reservoir port” is “implanted to encircle the top portion of the upper stomach creating a smaller stomach pouch.”<sup>213</sup> The Lap-Band can then be adjusted by deflating or further inflating the band with saline. In the event of complications or ineffectiveness, the Lap-Band can be removed. The removal procedure is typically laparoscopic—some can even be performed through a single incision.<sup>214</sup>

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210. This would present an opportunity for greater international cooperation among the FDA and foreign regulatory agencies, such as the European Medicines Agency, and international organizations, such as the World Health Organization. Similar initiatives have long been a goal for much of the international community. Ryan Abbott, *Overcoming Barriers to a Global Treaty on Medical Funding and R&D*, J. BRAZ. INST. FOR INTEL. PROP 70, 70–76 (2012).

211. The following metric is used to categorize patients: Underweight (<18.5 kg/m<sup>2</sup>), Normal (18.5 to 24.9 kg/m<sup>2</sup>), Overweight (25 to 29.9 kg/m<sup>2</sup>), Obesity I (30 to 43.9 kg/m<sup>2</sup>), Obesity II (35 to 39.9 kg/m<sup>2</sup>), and Extreme Obesity (≥ 40 kg/m<sup>2</sup>). See NAT’L HEART, LUNG, AND BLOOD INST., NAT’L INSTS. OF HEALTH, CLINICAL GUIDELINES ON THE IDENTIFICATION, EVALUATION, AND TREATMENT OF OVERWEIGHT AND OBESITY IN ADULTS: THE EVIDENCE REPORT xiv (1998), [http://www.nhlbi.nih.gov/guidelines/obesity/ob\\_gdlns.pdf](http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf). There are limits on the utility of BMI measurements, which do not, for example, account for muscularity or frame size. *Id.*

212. U.S. FOOD AND DRUG ADMIN., SYSTEMATIC LITERATURE REVIEW ON THE IMPACT OF WEIGHT LOSS FROM ADJUSTABLE GASTRIC BANDING ON DIABETES, HYPERTENSION, AND DYSLIPIDEMIA 1 (2000).

213. *Id.*

214. While a majority of Lap-Band removal surgeries are laparoscopic, a sizeable minority of patients undergoing removal surgery have to undergo “open” surgery, with a larger incision and recovery time. *Risks Associated with the Laparoscopic Adjustable Gastric Band*, MUSC HEALTH, <http://www.muschealth.com/weightlossurgery/about/procedures/laprisks.htm> (last visited Nov. 5, 2014) (“Laparoscopic surgery is not always possible. The surgeon may need to switch to an ‘open’ method . . .”).

Research suggests that the Lap-Band is effective in promoting weight loss. The Lap-Band was approved in part on the basis of a three-year, prospective, multicenter, nonrandomized trial with 299 subjects.<sup>215</sup> That study found that obese patients lost an average of 60 to 70 percent of their excess weight within one year after their Lap-Band surgery.<sup>216</sup> Eighty percent of all patients lost at least 30 percent of their excess weight and kept it off for one year.<sup>217</sup> In 2008, a meta-analysis evaluated 104 studies with more than 24,000 patients and found that patients' mean excess-weight loss three years after Lap-Band surgery was 50.2 percent.<sup>218</sup> The authors concluded that "gastric banding meta-analysis provided evidence that, as a bariatric procedure, LAGB safely achieves clinically significant, durable weight loss and comorbidity improvement."<sup>219</sup> In addition to being effective, the Lap-Band represented a significant improvement over prior, more invasive bariatric surgical options, which permanently reduced the size of the stomach and shortened the intestines.<sup>220</sup> A 2005 meta-analysis of 147 studies on surgical treatment of obesity compared the most common gastric bypass procedure (Roux-en-Y gastric bypass) with gastric band surgery.<sup>221</sup> The patients who

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215. The mean excess-weight loss (EWL) one year post-Lap-Band for patients whose starting BMI was equal to, or greater than, 35 was 60.88 percent with comorbidities and 61.65 percent without comorbidities; the EWL for patients with a BMI less than 35 was 69.34 percent with comorbidities and 67.57 percent without comorbidities. U.S. FOOD AND DRUG ADMIN., THE LAP-BAND ADJUSTABLE GASTRIC BANDING SYSTEM, SUMMARY OF SAFETY AND EFFECTIVENESS DATA, at 28 tbl.16 (2011), [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/P000008S017b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P000008S017b.pdf). The total sample size was 149 patients: 56 patients had a BMI less than 35 with comorbidities; 8 patients had a BMI less than 35 without comorbidities; 71 patients had a BMI of 35 or more with comorbidities patients; and 14 patients had a BMI of 35 or more without comorbidities. *Id.*

216. *Id.*

217. Press Release, U.S. Food & Drug Admin., FDA Expands Use of Banding System for Weight Loss (Feb. 16, 2011). The FDA used the 1983 Metropolitan Life Insurance Tables to determine "estimated ideal weight," instructing users to "use the midpoint for medium frame." See U.S. FOOD AND DRUG ADMIN., *supra* note 215, at 1.

218. Scott A. Cunneen, *Review of Meta-Analytic Comparisons of Bariatric Surgery with a Focus on Laparoscopic Adjustable Gastric Banding*, 4 SURG. FOR OBES. AND RELAT. DIS. S47-S55, S49 (2008).

219. *Id.*

220. U.S. FOOD & DRUG ADMIN., *supra* note 215. Two types of gastric bands have been approved for use in the United States: the Lap-Band Gastric Banding System and the Realize Gastric Band. *Obesity Treatment Devices: FDA Approved Obesity Treatment Devices*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ObesityDevices/ucm350134.htm> (last updated July 8, 2014).

221. Melinda A. Maggard et al., *Meta-Analysis: Surgical Treatment of Obesity*, 142 ANN. INTERN. MED. 547, 547-59 (2005).

underwent gastric bypass had a mortality rate of 0.3 percent across case series, whereas those who had gastric banding had a 0.02 percent mortality rate.<sup>222</sup> However, Lap-Band does cause a high rate of adverse events. Complications affect a majority of those who have a Lap-Band implanted: “more than 70 percent of patients experienced an adverse event related to LAP-BAND, most often vomiting and difficulty swallowing. The events ranged from mild to severe but most were mild and resolved quickly.”<sup>223</sup> Other potential problems include infection, port-related complications, slippage, pouch dilation, stomach ischemia, and erosion.<sup>224</sup> A 2011 search of the FDA adverse-events database for Lap-Bands revealed more than eight-thousand adverse-event reports, including eighty deaths.<sup>225</sup>

The Lap-Band became available outside the United States in July 1994, and the FDA approved domestic clinical trials in 1995.<sup>226</sup> An estimated fifty thousand patients received a Lap-Band outside the United States<sup>227</sup> prior to its FDA approval in 2001.<sup>228</sup> As a condition of approval, the product sponsor agreed to continue tracking patients from the approval trials for a total of five years of follow up.<sup>229</sup> Initially, the FDA approved Lap-Bands only in “severely obese patients with a Body Mass Index (BMI) of at least 40 or a BMI of at least 35 with one or more severe comorbid conditions, or those who are 100 lbs. or more over their estimated ideal weight.”<sup>230</sup> Additional criteria included a documented history of failed conservative weight-

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222. *Id.* at 553 (“The early mortality rate for RYGB was 1.0% (95% CI, 0.5% to 1.9%) in controlled trials and 0.3% (CI, 0.2% to 0.4%) for case series data. Adjustable gastric banding had an associated early mortality rate of 0.4% (CI, 0.01% to 2.1%) for controlled trials and 0.02% (97.5% CI, 0% to 0.78%) for case series data.”).

223. Press Release, U.S. Food & Drug Admin., *supra* note 217.

224. Sandra Arthurs, Yerado Abrahamian, Elizabeth L. Loughren, Jo Carol Hiatt, Robin Cisneros & Jed Weissberg, *New Technology Review Process: The Laparoscopic Adjustable Gastric Band*, 15 THE PERMANENTE J. 4, 56 (Fall 2011).

225. *Id.*

226. M. Belachew, M. J. Legrand & V. Vincent, *History of Lap-Band®: From Dream to Reality*, 11 OBESITY SURGERY 297, 301–02 (2001).

227. *Id.*

228. Letter from Daniel G. Schultz, Deputy Dir. for Clinical and Review Policy, to Ellen Duke, President and Chief Exec. Officer, BioEnterics Corp. (Mar. 24, 2000) (amended Apr. 20, 2000; May 3, 2000; Dec. 26, 2000; May 18, 2001; and June 1, 2001), [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/p000008a.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/p000008a.pdf).

229. *Id.* (“You agreed to continue follow-up on subjects enrolled . . . [in] your investigational study. These post-approval subjects must be followed for a total of 5 years from the time of implantation. . . . The results of the post-approval study should be reflected in the labeling via a PMA supplement when the study is complete.”).

230. *Id.*

reduction alternatives and a lifetime commitment to change one's eating habits.<sup>231</sup> The FDA expressed caution in its letter of approval, stating that the Lap-Band should be a last resort.<sup>232</sup> It was not until February 2011 that the FDA expanded the use of the Lap-Band to patients with BMIs as low as 30 if they presented with severe conditions such as heart disease or diabetes, which put them at the "highest risk of obesity-related complications."<sup>233</sup> This was narrower than the indication originally sought by Allergan, which had proposed expanding use of the Lap-Band to patients with BMIs from 35 to 39 without obesity-related conditions.<sup>234</sup> The Lap-Band is still not recommended "for non-adult patients, patients with conditions that may make them poor surgical candidates or increase the risk of poor results . . . who are unwilling or unable to comply with the required dietary restrictions, who have alcohol or drug addictions, or who currently are or may be pregnant."<sup>235</sup>

Since the device's approval, there has been strong consumer demand for off-label use.<sup>236</sup> That is evidenced, for example, by the agency's difficulties contending with "pop-up"-type ambulatory surgical firms marketing aggressively and promising unrealistic results with little to no mention of accompanying dietary restrictions, post-surgical compliance, or the Lap-Band's potential complications. For example, one weight-loss-surgery business used a "1-800-GET-THIN" marketing campaign in Southern California.<sup>237</sup> That campaign utilized advertisements inserts such as "LOSE WEIGHT WITH THE LAP-BAND! SAFE 1 HOUR, FDA APPROVED," "Celebrate Black History Month! Let Your New Life Begin! 1-800-GET-THIN,"

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231. U.S. FOOD & DRUG ADMIN., *supra* note 215.

232. Letter from Daniel G. Schultz, Deputy Dir. for Clinical and Review Policy, to Ellen Duke, President and Chief Exec. Officer, BioEnterics Corp., *supra* note 228.

233. Press Release, U.S. Food and Drug Admin., *supra* note 217.

234. *Id.*

235. Find a LAP-BAND® Specialist, LAP-BAND SYSTEM, <http://www.lapband.com/find-a-specialist> (last visited Nov. 15, 2014).

236. In one study of "208 participants . . . 49 (23.6%) rated appearance, 18 (8.7%) embarrassment, 49 (23.6%) medical condition, 59 (28.4%) health concerns, 13 (6.3%) physical fitness and 20 (9.6%) physical limitation as the most appropriate motivational statement." Marije Libeton, John B. Dixon, Cheryl Laurie & Paul E. O'Brien, *Patient Motivation for Bariatric Surgery: Characteristics and Impact on Outcomes*, 14 OBES. SURG. 392, 392 (2004).

237. See Letter from Steven D. Silverman, Dir. of the Office of Compliance of the Ctr. for Devices and Radiological Health, U.S. Food and Drug Admin., to Robert Silverman, Esq., of 1-800-GET-THIN, LLC (Dec. 12, 2011), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm283312.htm> (describing various violations related to advertising campaigns run by 1-800-GET-THIN).

and promising testimonials, such as “MARCIANO LOST 125 POUNDS.”<sup>238</sup> That group claimed that facilities associated with the campaign were “bringing in \$21 million a month” in revenue.<sup>239</sup> On December 11, 2011, the FDA cautioned the group behind “1-800-GET-THIN” that its advertisements “fail to reveal material facts, including relevant risk information regarding the use of the Lap-Band, age and other qualifying requirements for the Lap-Band procedure, and the need for the ongoing modification of eating habits, as provided in the approved Lap-Band labeling.”<sup>240</sup> That same day, several such notices were also sent to related groups heavily promoting the Lap-Band.<sup>241</sup>

#### D. *The Lap-Band Dynamic Extrapolation Approach*

The Lap-Band presents numerous regulatory extrapolation challenges. First, at what BMI should the Lap-Band be used? Was the FDA too cautious in its earlier BMI indications? Is it still being too cautious? Should comorbidities be required at lower BMIs? Is there a legitimate rationale for approval for a BMI of 40 but not 39? Second, in what populations should the Lap-Band be used? Should it be approved in pediatric populations?<sup>242</sup> Is there an age after which the risks of the device outweigh the benefits? Should it be used in pregnant patients? Should it be used in patients who have comorbidities (for example, a history of mental illness) that cause them to be excluded from clinical trials? Third, should the Lap-Band be used indefinitely given that the device was only studied for five years? Fourth, should alternative medical devices, such as the Realize

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238. *Id.*

239. Stuart Pfeifer, *800-GET-THIN Probe Intensifies*, L.A. TIMES, June 4, 2014, <http://www.latimes.com/business/la-fi-omidi-search-warrant-20140605-story.html>.

240. Letter from Steven D. Silverman, Dir. of the Office of Compliance of the Ctr. for Devices and Radiological Health, U.S. Food and Drug Admin., to Maria Abaca, of Beverly Hills Surgery Center LLC (Dec. 9, 2011), <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm283310.htm>.

241. Stuart Pfeifer, Duke Helfand & W.J. Hennigan, *FDA Accuses 1-800-GET-THIN of Using Misleading Lap-Band Ads*, L.A. TIMES, Dec. 14, 2011, <http://articles.latimes.com/2011/dec/14/business/la-fi-lap-band-fda-20111214>.

242. Lap Band is not currently FDA-approved for use in patients younger than eighteen. Mikaela Conlet, *Lap Band Surgery: Allergan Asks FDA to Approve Obesity Surgery for Teens*, ABC NEWS (May 25, 2011), <http://abcnews.go.com/Health/lap-band-maker-allergan-hopes-offer-surgery-teens/story?id=13678820>.

Band, which is manufactured by Ethicon Endo-Surgery, Inc.,<sup>243</sup> be approved based on data for the Lap-Band?

Our Lap-Band case study will discuss only a few of these extrapolation issues: duration of treatment, follow-on device approval, and BMI indication. Again, our approach begins with data collection. Extrapolation determinations would be improved with data that has not been systematically collected or analyzed, but that would have been under our framework.

With regard to duration of treatment, there is currently no evidence that would support limiting the Lap-Band's duration. Moreover, limiting the device's duration of treatment would require a second surgery to remove the device. At present, clinical guidelines suggest Lap-Band patients should be seen by a physician three to eight times the first year, one to four times the second year, and one to two times every year thereafter.<sup>244</sup> However, given that patients are using this device indefinitely and that the device has been studied only for five years in a controlled setting, our framework would place a burden on the manufacturer to continue patient follow-up from controlled trials indefinitely. Such follow-up might detect new risks that emerge more than five years after device implantation, or it might find that known risks become more prevalent years after device implantation. That evidence would be collected and analyzed together with a more robust dataset from clinical practice. At present, there is inadequate safety data for the Lap-Band in light of its actual duration of use.<sup>245</sup>

Lap-Band data was appropriately extrapolated to the Realize Adjustable Gastric Band. The Realize Band, manufactured by Ethicon, has been marketed in Europe since 1996.<sup>246</sup> It became available to the European Union and other countries, excluding the United States, in 2004.<sup>247</sup> It was then approved by the FDA on

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243. *REALIZE Adjustable Gastric Band*, ETHICON ENDO-SURGERY, INC. (2009), <http://www.ethicon.com/sites/default/files/loose-documents/09-1089.pdf>.

244. S. Sauerland et al., *Obesity Surgery: Evidence-Based Guidelines of the European Association for Endoscopic Surgery (E.A.E.S.)*, 19 *SURGICAL ENDOSCOPY* 200, 200–21 (2005).

245. Arthurs et al., *supra* note 224, at 56.

246. U.S. FOOD & DRUG ADMIN., *REALIZE ADJUSTABLE GASTRIC BAND, SUMMARY OF SAFETY AND EFFECTIVENESS DATA 4* (2007), <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM302775.pdf>.

247. *Id.*

September 28, 2007.<sup>248</sup> Its parameters resemble the original Lap-Band indications: a BMI of 40 or greater, or a BMI of 35 or greater plus a comorbidity.<sup>249</sup> In addition to a review of Lap-Band data and data from the Realize Band's international use, the FDA required a three-year U.S. clinical study. That study implanted the Realize Band in 276 patients with at least a five-year history of morbid obesity who had exhausted nonsurgical weight-reduction efforts.<sup>250</sup> The results and adverse events were comparable to those of the Lap-Band.<sup>251</sup> The FDA also required a postapproval study with five years of follow-up.<sup>252</sup> Given a lack of evidence to suggest a clinical difference between the Lap-Band and the Realize Band, it would appear appropriate for the FDA to approve the Realize Band for the same indications as the Lap-Band, but to require Ethicon to continue monitoring its trial patients. Expanded data collection will be able to alert the FDA to risks if a significant difference emerges between the two devices in practice.

Determining the appropriate BMI indication is more challenging. The following factors are relevant: First, the amount of off-label use has not been well quantified, but there are indications that Lap-Band was commonly used outside of its approved BMI.<sup>253</sup> Second, off-label use here is along a continuous variable (BMI) and small in magnitude. Third, adverse events were relatively frequent and ranged from mild to severe. Fourth, there is a large population of

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248. *Id.*

249. Realize Patient Guide, ETHICON ENDO-SURGERY, available at [https://www.jnjgatewayifu.com/eLabelingContent/Ees/USENG/IFU\\_74120\\_Rev\\_A\\_REALIZE\\_PATIENT\\_GUIDE\\_44365.pdf](https://www.jnjgatewayifu.com/eLabelingContent/Ees/USENG/IFU_74120_Rev_A_REALIZE_PATIENT_GUIDE_44365.pdf) (2008).

250. All were at least one-hundred pounds overweight or 1.5 times their ideal body weight (IBW), from eighteen to sixty years of age, with a BMI greater than or equal to 40, or a BMI of 35 and an obesity-related comorbidity. Subjects were observed for three years: their mean EWL was 38 percent after one year; 44.7 percent after two years, and 41.1 percent at the end of the three years. The trial defined comorbidities as "type 2 diabetes, hyperlipidemia, obstructive sleep apnea, hypertension, metabolic syndrome, or osteoarthritis of the hip or knee" that "were generally expected to be improved, reversed, or resolved by weight loss." U.S. FOOD & DRUG ADMIN., *supra* note 246, at 15.

251. *Id.*

252. *Id.*

253. See, e.g., Kathleen Doheny, *Bariatric Surgery Helps People Who Are Less Obese*, WEBMD (June 16, 2011), <http://www.webmd.com/diet/weight-loss-surgery/news/20110616/study-bariatric-surgery-works-for-less-obese-people>; T.H. Inge, S.A. Xanthakos & M.H. Zeller, *Bariatric Surgery for Pediatric Extreme Obesity: Now or Later?*, 31 INT'L J. OBESITY 1 (2007); Paul E. O'Brien et al., *Laparoscopic Adjustable Gastric Banding in Severely Obese Adolescents: A Randomized Trial*, 303 JAMA 6, 519-26 (2010) (describing a study using the Lap-Band in which the participants had a BMI of 35 or higher, but did not necessarily have a comorbidity).



potential off-label users. Fifth, the Lap-Band treats obesity and related comorbidities, including type 2 diabetes, high blood pressure, high cholesterol, and obstructive sleep apnea, which are serious conditions. Sixth, unlike traditional and irreversible bariatric surgeries, the Lap-Band procedure is reversible.

Our framework suggests that the FDA may have been too cautious with its initial approval of Lap-Band—which limited the device to patients with a BMI of 40, or 35 with one or more severe comorbid conditions. Off-label use for a lower BMI is along a continuous variable; absent data suggesting a sudden shift in outcomes between a BMI of 34 and 35, there is not necessarily a strong theoretical justification for that cutoff. Further, this off-label use is occurring in the “hump” of the distribution. The extrapolation population size of off-label users is sufficiently large to ensure a vibrant dataset for postmarket data collection. As opposed to conventional irreversible surgeries, in the event postmarket data revealed unexpected risks related to Lap-Band, the device could be removed. Our framework suggests that the Lap-Band could have been initially approved for either its 2011 indication, namely patients with a BMI of 30 to 34 presenting the highest risk of obesity-related complications, or its 2013 indications, namely patients with a BMI of 30 to 40 with at least one obesity-related comorbidity. Our framework would also put a higher burden on manufacturers to conduct postmarket studies in these populations. The FDA could have approved the device for lower BMIs as conditional off-label uses, subject to the product sponsor completing its PMR according to agreed-upon timelines.

Extrapolation from more comprehensive data on off-label use might have permitted earlier expansion of Lap-Band indications and earlier approval of the Realize Band. Approval of the Lap-Band for a lower BMI would have allowed more patients to benefit at an earlier stage of obesity. Approval of the Realize Band at an early stage might also have lowered healthcare costs by facilitating competition.

#### CONCLUSION

This Article has argued for an evolutionary approach to drug and medical device regulation. Our goal has been to move evidence-based policymaking toward Bayesianism. At its most fundamental level,

Bayes' Law is the science of learning.<sup>254</sup> To apply Bayesian decisionmaking, one needs to form a prior belief based on existing evidence, gather additional information, and then update the prior belief.<sup>255</sup> Our proposals are Bayesian because they force policymakers to assess and acknowledge the imperfect nature of their prior beliefs; gather, when cost-effective, additional information; and take action in terms of approvals, reimbursements, and enforcement based on continual updating. This Article advocates putting Bayesianism into regulatory practice.

Although we have focused our attention on FDA regulations, our evolutionary evidence-based approach to policymaking has application to virtually any area of government decisionmaking. For example, the National Transportation Safety Board has recommended that states consider a kind of criminal-law extrapolation that would expand the scope of Driving Under the Influence (DUI) liability by lowering the blood-alcohol level that would trigger a criminal violation.<sup>256</sup> In fact, one can imagine DUI extrapolations that would be directly analogous to the four forms of medical extrapolation discussed above. First, "diagnosis extrapolation" occurs when the coverage (elements) of a crime are expanded to punish related behaviors (for example, expanding DUI laws to cover different blood-alcohol levels or to cover additional drugs). Second, "patient extrapolation" occurs when the coverage (elements) of a crime are expanded to punish a new population (for example, expanding DUI laws to cover younger drivers). Third, "dosage extrapolation" occurs when the punishments' durations are changed (for example, altering the DUI punishment by changing the length of incarceration or suspending licenses). Finally, "treatment extrapolation" occurs when the punishments are changed to related kinds of interventions (for example, changing the content of mandatory driver-education classes, or the conditions of imprisonment or supervised release). Any legal reform that extrapolates the size of a mandate, the class to which it applies, or the consequences of noncompliance, might be ripe for our evolutionary evidence-based approach.

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254. See JACKMAN, *supra* note 11.

255. See Simon Jackman, *Bayesian Analysis for Political Research*, 7 ANN. REV. POL. SCI. 483, 483 (2004); see also JACKMAN, *supra* note 11.

256. NAT'L TRANS. SAFETY BD., REACHING ZERO: ACTIONS TO ELIMINATE ALCOHOL-IMPAIRED DRIVING (May 14, 2013), <http://www.nts.gov/doclib/reports/2013/SR1301.pdf> (last visited Nov. 5, 2014).

Just as the FDA sometimes requires drug testing before regulatory approval, lawmakers at times should test legal reforms before enactment. Indeed, one of us has argued that we should sometimes “randomize law”—that is, lawmakers should conduct randomized controlled trials to assess the causal impact of legal reform before adopting a reform on a permanent basis.<sup>257</sup> But at other times, the urgency of the present precludes gathering all relevant evidence before enactment. In such circumstances, evidentiary extrapolation coupled with dynamic, Bayesian updating is the best way forward.

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257. See Ian Ayres, Yair J. Listokin & Michael Abramowicz, *Randomizing Law*, 159 U. PA. L. REV. 929, 1005 (2011) (“Randomized experimentation offers a powerful means to evaluate the effects of proposed policies. By applying laws and policies to different groups on a random basis, the causal impacts of the law can be isolated from other factors that would ordinarily be correlated with exposure to different policies.”); see also Miguel F. P. de Figueiredo, *Throw Away the Jail or Throw Away the Key?: The Effect of Punishment on Recidivism and Social Cost 1* (June 21, 2014) (unpublished manuscript) (<http://extranet.isnie.org/uploads/isnie2014/de-figueiredo.pdf>) (examining “the effectiveness of . . . sanctions in curbing recidivism and vehicle crashes with some 200,000 alcohol tests”).