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The Law, Economics, and Medicine of Off-Label Prescribing

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THE LAW, ECONOMICS, AND MEDICINE OF OFF-LABEL PRESCRIBING

William S. Comanor* & Jack Needleman**

Abstract: There is a major dissonance in the current structure of regulating new drugs that have more than one medical indication. Physicians are authorized to prescribe these drugs for all indications including those beyond their approved purposes. However, product manufacturers are expressly prohibited from marketing or promoting their drugs for any purpose other than those which have been specifically indicated. While prescribing physicians are encouraged to gain medical information on any additional indications, they cannot obtain it from one of its most likely sources: the drug's supplier.

The Second Circuit Court of Appeals' recent opinion in *United States v. Caronia* has challenged this regulatory structure. For the three states in the Second Circuit, although not the rest of the country, the FDA's regulations prohibiting promotion of non-approved indications have been restricted.

In this Article, we review the legal, economic, and medical aspects of the FDA's current regulatory approach, and explore the likely consequences of a widespread adoption of the *Caronia* rule.

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INTRODUCTION

There is a major dissonance in the current structure of regulating new drugs that have more than a single medical indication. Physicians are authorized to prescribe these drugs for all indications including those

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beyond their approved purposes. However, product manufacturers are expressly prohibited from marketing or promoting their drugs for any purpose other than those which have been specifically indicated.¹ Thus, while prescribing physicians are encouraged to gain medical information on any additional indications, the information that physicians can obtain from the most likely source—the drug’s supplier—is substantially constrained.²

Although the Food and Drug Administration (FDA) originally accentuated this dissonance, it has more recently retreated from that posture; first under pressure from the statutory admonitions of 1997,³ and subsequently due to the Second Circuit’s opinion in *United States v. Caronia*.⁴ However, the issue remains in flux and is the subject of this Article.

In succeeding Parts, we review the legal, economic, and medical aspects of this dissonance: between what physicians are authorized to prescribe and what information drug manufactures are permitted to provide about their products. A critical feature of this dissonance is its connection to the two separate types of information about the therapeutic properties of pharmaceuticals, so we start with a discussion of this distinction. Finally, we suggest some policy conclusions to be drawn for this discussion.

I. PHARMACEUTICAL EFFICACY AND EFFECTIVENESS

The U.S. drug approval process is a multi-stage process involving the identification of a potential drug and various trials that must be met to discern its safety and efficacy. The formal approval process requires manufacturers to submit a New Drug Application (NDA), which the FDA reviews in its decision-making process on whether to approve a drug for sale. Critically, drugs are approved only for the specific indications disclosed in the firm’s NDA.

An essential part of the NDA is its report on the three formal stages of testing required by the FDA. Phase I, usually conducted on healthy volunteers, focuses on safety and potential side effects, and may also be used to understand how the drug is metabolized.⁵ Phase II examines

1. *United States v. Caronia*, 703 F.3d 149, 154–55 (2d Cir. 2012).

2. *See id.*

3. Food and Drug Administration Modernization Act of 1997, 21 U.S.C. § 301 (2012).

4. 703 F.3d 149 (2d Cir. 2012).

5. U.S. FOOD & DRUG ADMIN., DRUG APPROVAL PROCESS, <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf> [<https://perma.cc/5DGM-BEB6>].

whether the drug appears to be effective for a specific indication, where the proposed drug is compared to a placebo or another drug.⁶ Safety and side effects continue to be assessed in these trials.⁷ Phase III is a much larger trial which assesses the efficacy of the drug in different subpopulations and at different dosages.⁸ Such trials can vary in their complexity, but their inferences of efficacy are fundamentally based on the statistical tests of the differences in outcomes in the patients treated with the drug and those treated with placebos or alternatives.⁹ Given the expense of Phase III trials and the numbers of patients required to assure that differences in outcomes are unlikely to be the results of sampling variation between the treated and control groups, the outcomes and indications studied in these trials are often quite limited.¹⁰

At the heart of the ongoing policy debates concerning off-label prescribing lies the distinction between pharmaceutical “efficacy” and “effectiveness.” That distinction follows from the different types of information that can potentially be gleaned on the therapeutic benefits gained from taking pharmaceuticals. Consider the difference between the information obtained from a formal clinical trial of a prospective drug and the information gathered from medical practice and experience resulting largely from observational studies.

The clinical trials required by the FDA to be included in a company’s NDA make little use of any substantive knowledge of the drugs being studied. The judgment that a drug is efficacious or not is based on the results of a randomized control trial, in which judgments on efficacy are made by ruling out, via statistical theory, that difference in outcomes between the treatment and control group are simply due to sampling variation.¹¹ Randomization is presumed sufficient to balance the observable and unobservable factors that might influence outcomes.¹² And confidence in the results is enhanced by including only a narrow group of patients with limited variation in key characteristics and by maintaining high standards for protocol fidelity.¹³ To a great extent, the

6. *Id.*

7. *Id.*

8. *Id.*

9. *Id.*; see also G.R. Davies et al., *Adaptive Clinical Trials in Tuberculosis: Applications, Challenges and Solutions*, 19 INT’L J. TUBERCULOSIS & LUNG DISEASE 626 (2015).

10. U.S. FOOD & DRUG ADMIN., *supra* note 5; Davies et al., *supra* note 9.

11. Kenneth Stanley, *Design of Randomized Controlled Trials*, 115 CIRCULATION 1164, 1166 (2007).

12. *Id.*

13. *Id.*

fundamental discipline underlying the trials is not pharmacology but statistics.

In contrast, assessments of a drug's effectiveness rely on experience and medical observation in patient populations.¹⁴ Understanding the mode of action of the underlying active ingredient can be critical in a clinician's judgment about whether a particular use is appropriate, and these judgments are refined by extension to other settings. Note that this reliance typically requires a clear understanding of the drug's pharmacology.

Both methods have their strengths and their weaknesses. The clinical trials used to demonstrate a drug's efficacy depend critically on the sample of patients being tested. Clinical trials strictly pertain only to the population from which the sample is drawn. If the results are extrapolated or generalized to apply to populations beyond those included in the clinical trial, the therapeutic effects found in the clinical trials may not apply. Furthermore, statistical tests are generally applied to mean values which can be misleading when the variance of individual outcomes is large. For drugs which are effective only for a limited segment of the patient population, moreover, the positive effect on that segment may be obscured by the drug's unresponsiveness in the rest of the population.

In addition, statistical tests require the selection of a particular level of statistical significance, which in effect defines the trade-off between Type I and Type II errors.¹⁵ Because of the influence of random or

14. To make this concrete, consider the report of the trial of sofosbuvir (sovaldi) for untreated chronic hepatitis C infection, as reported in the *New England Journal of Medicine*. Eric Lawitz et al., *Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection*, 20 *NEW ENG. J. MED.* 1878 (2013). The analysis section describing the methods reads in part:

In the NEUTRINO study, we determined that the enrollment of 300 patients with HCV genotype 1, 4, 5, or 6 infection would provide a power of 90% to show a rate of sustained virologic response with the sofosbuvir regimen that was higher than 60%, a calculated control rate based on previous efficacy after adjustment for the presence of cirrhosis and expected safety benefit.

Id. at 1880. "We used two-sided testing at the 0.05 level in both studies. Multivariable logistic-regression analyses characterizing the relationship between a sustained virologic response and various prespecified demographic and baseline clinical characteristics were performed." *Id.* at 1880–81. The results section reads:

A total of 295 of the 327 patients (90%; 95% confidence interval [CI], 87 to 93) with HCV genotype 1, 4, 5, or 6 had a sustained virologic response 12 weeks after treatment (Table 2). The two-sided one-sample exact test established the primary efficacy end point of the superiority of sofosbuvir plus peginterferon-ribavirin, as compared with an adjusted historical response rate of 60% ($P < 0.001$).

Id. at 1881. Some laboratory results are reported on patients who relapsed after treatment, but this is a limited part of the trial and not central to the decision to approve the drug. *Id.* at 1883.

15. A type I error is an incorrect rejection of the null hypothesis (false positive). J.A. Freiman et al., *The Importance of Beta, the Type II Error and Sample Size in the Design and Interpretation of*

individual factors, minimizing the risk of approving an inefficacious drug means tolerating increased risks of disapproving efficacious drugs. The need to select among these types of error is an inevitable attribute of employing statistical methods for drug approval. Moreover, the level of statistical significance is typically fixed by standard practice without regard to the potential risks and benefits of a particular drug.

In contrast, relying on observational data has its own problems. Outcomes invariably depend on the particular patients observed, and one never knows whether a specific patient is typical or not. In addition, patients in observational studies are not selected randomly so that judgments of a drug's effectiveness may require dealing with substantial variation among patients along with differences in dosages as well as between planned and actual use of dosage regimens.¹⁶ As a result, the patient outcomes in observational studies may not represent the typical response to the drug. The relevant information includes both case reports and trials noted in the medical literature. These studies rely on an understanding of medical modes of action so there is more than mere statistics involved. In determining drug effectiveness, pharmacological understanding plays a major role.

For new pharmaceuticals, the clinical trial data contained in the NDA is the only available basis for assessing efficacy. On the other hand, for drugs already on the market that may have been used extensively by physicians for non-indicated purposes, the medical literature is a prominent source of product information. Critically, judgments based on these different types of information can be quite different. The discrepancies between a drug's performance in clinical trials—its efficacy—and its performance in a larger patient population—its effectiveness—have been regularly noted in the medical literature.¹⁷

the Randomized Control Trial: Survey of 71 "Negative" Trials, 299 NEW ENG. J. MED. 690, 690 (1978). A type II error is a failure to reject a false null hypothesis (false negative). *Id.* at 691. In the case of a prescription drug, a type I error would be drawing a conclusion that the drug has an effect different from the placebo or other treatment it is being tested against. *Id.* at 690. A type II error would be concluding the effect is absent when in the population it is present. *Id.* at 691. There is a tradeoff between these types of errors with the degree of the tradeoff and risk of each error a function of the magnitude of the effectiveness of the drug in the population (compared to placebo or comparison treatment) and the size of the samples in which the test is conducted. See Milton Weinstein & Richard Zeckhauser, *Critical Ratios and Efficient Allocation*, 2 J. PUB. ECON. 147, 154 (1973).

16. Anders Ahlbom, *Statistical and Scientific Inference*, 276 J. INTERNAL MED. 238 (2014); Natalie A. DiPietro, *Methods in Epidemiology: Observational Study Designs*, 30 PHARMACOTHERAPY 973 (2010); Kelly M. Shields et al., *Principles of Drug Literature Evaluation for Observational Study Designs*, 31 PHARMACOTHERAPY 115 (2011).

17. See, e.g., Hans-Georg Eichler et al., *Bridging the Efficacy-Effectiveness Gap: A Regulator's*

Assessments of the appropriateness of using a drug based on clinical trials may well differ from decisions based on experience gained from off-label monitoring and less controlled, more observational studies.

As off-label uses are reported, drug compendia evaluate the available evidence and present an assessment of appropriate uses.¹⁸ These compendia are summaries of drug information compiled by a wide range of non-government parties, drawing upon internal experts and external reviewers. They include information on drug characteristics, recommended uses, and dosages. Payers¹⁹ use compendia assessments to determine whether a given use will be reimbursed.²⁰ Potential reimbursement may also affect physician prescription patterns.²¹

In some medical specialties, it is common for the professional association or academy to publish accepted practice guidelines. Thus, before deciding whether to prescribe a drug for a specific off-label use, clinicians may reference their own experience, published literature, compendia or local or professional guidelines, and payer policies toward reimbursing for specific purposes.²² Over time this information base can grow, providing new assessments of both the efficacy of a drug as demonstrated in clinical trials in a limited population and also potentially the effectiveness of the drug as used in practice across broader patient populations.²³

Perspective on Addressing Variability of Drug Response, 10 NATURE REVS. DRUG DISCOVERY 495 (2011).

18. Loreen Brown, *Gain a Solid Understanding of Compendia and Its Impact on Patient Access*, FORMULARY WATCH 252–56 (2012), <http://formularyjournal.modernmedicine.com/formulary-journal/news/clinical/clinical-pharmacology/gain-solid-understanding-compendia-and-its-imp> [<https://perma.cc/3C26-VN4K>].

19. Payers include insurance companies, large corporations, government agencies, such as the Centers for Medicare and Medicaid Services, and others who pay pharmacies the larger share of the pharmaceuticals used by on behalf of insured patients.

20. ROSS MCKINNEY ET AL., DUKE CTR. FOR CLINICAL HEALTH POLICY RES., POTENTIAL CONFLICT OF INTEREST IN THE PRODUCTION OF DRUG COMPENDIA 5 (2009), www.amcp.org/WorkArea/DownloadAsset.aspx?id=9442 [<https://perma.cc/F2B3-QQ3V>].

21. See generally William H. Shrank et al., *A Bitter Pill: Formulary Variability and the Challenge to Prescribing Physicians*, 17 J. AM. BOARD FAM. PRAC. 401, 401 (2004).

22. See generally N. Ghinea et al., *No Evidence or No Alternative? Taking Responsibility for Off-Label Prescribing*, 42 J. INTERNAL MED. 247 (2012); Emily A. Largent et al., *Going Off-Label Without Venturing Off-Course: Evidence and Ethical Off-Label Prescribing*, 169 ARCHIVES INTERNAL MED. 1745 (2009).

23. Brian R. Flay, *Efficacy and Effectiveness Trials (and Other Phases of Research) in the Development of Health Promotion Programs*, 15 PREVENTIVE MED. 451 (1986); Russell E. Glasgow et al., *Why Don't We See More Translation of Health Promotion Research to Practice? Rethinking the Efficacy-to-Effectiveness Transition*, 93 AM. J. PUB. HEALTH 1261 (2003).

II. THE LAW AND REGULATION OF PRODUCT LABELING

Under the Food, Drug, and Cosmetic Act (FDCA),²⁴ the FDA is authorized to regulate and control pharmaceutical labeling,²⁵ and it is this authority that serves as the basis for the agency's post-market regulation. Once the FDA has approved a pharmaceutical for sale, it cedes substantial control over the drug to the approved manufacturer, who is then free to price and distribute the product largely as it wants. However, the FDA retains control over product labeling.²⁶

For decades, the FDA has required that the drug labels of approved drugs follow the format contained in its "Uniform Labeling Requirements."²⁷ Among the subjects to be included in a drug's label are its "indications and usage;" information which is derived directly from the seller's approved NDA.²⁸ Furthermore, as one writer noted, "the emergent irony of prescription drug labeling . . . is that it increasingly depends upon pre-market decision-making rather than post-market surveillance."²⁹ In large measure, the decisions a pharmaceutical company makes in the pre-licensure period regarding which indications and endpoints are the focus of its clinical trials determine the approved labeled indications and usage. Strikingly, the drug's history in use has only a minimal effect on product labeling, which instead depends largely on the trials reported in the drug's NDA that were completed before the product was authorized for sale.³⁰

The FDA's authority over pharmaceutical labeling could potentially be exercised over both physicians and manufacturers. However, the FDA has recognized that its authority diminishes once new drugs are approved.³¹ Whether for political or medical reasons, the agency has traditionally considered regulating the prescribing decisions of physicians as beyond its mandate. Its guidance to physicians on this issue reads: "[i]f physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed

24. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–399(f) (2012). The FDCA was signed in 1938 by President Roosevelt. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040.

25. DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 114, 116 (2010).

26. *Wash. Legal Found. v. Kessler*, 880 F. Supp. 26, 30 (D.D.C. 1995).

27. CARPENTER, *supra* note 25, at 614–15.

28. *Id.* at 615.

29. *Id.* at 615–16.

30. *Id.*

31. *Id.* at 608–09.

about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."³²

This regulatory posture has accompanied widespread off-label prescribing and use. While there are no definitive values for the proportion of prescriptions written off-label, estimates range from twenty-one to sixty percent of all prescriptions.³³ There are three types of off-label use: prescription of the drug for patients for whom it has not been approved, especially children; application at doses or through modes of administration that have not been approved; and prescription for conditions for which the drug has not been approved.

Among the more common off-label uses for drugs are for the treatment of children, and those directed at psychiatric and neurological disorders, and cancer. The extent of off-label use in children has been widely studied in both inpatient and outpatient settings. In a 2005 review of thirty studies on off-label drug use in children, the authors reported that off-label prescribing varied from eleven to eighty percent.³⁴ Rates were higher for inpatients than outpatients, and higher for younger children. In neonatal units, rates of off-label prescribing ranged from fifty-five to eighty percent, while in other hospital units, off-label prescribing ranged from sixteen to sixty-two percent.³⁵ On the other hand, in outpatient and community hospital settings, the reported rate of off-label prescribing ranged from eleven to thirty-seven percent.³⁶ A 2009 study using the U.S. National Ambulatory Care Medical Survey found that sixty-two percent of outpatient pediatric visits included off-label prescribing.³⁷

No comparable studies exist for psychiatric care, but there are some reports of the use of antipsychotic agents, which find rates of off-label prescribing between fifteen and sixty-six percent.³⁸ In a review of off-

32. U.S. FOOD & DRUG ADMIN., OFF-LABEL AND INVESTIGATIONAL USE OF MARKETED DRUGS, BIOLOGICS, AND MEDICAL DEVICES – INFORMATION SHEET (2014).

33. James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 80 (1998); David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1024 (2006).

34. Chiara Pandolfini & Maurizio Bonati, *A Literature Review on Off-Label Drug Use in Children*, 164 EUR. J. PEDIATRICS 552, 552 (2004).

35. *Id.*

36. *Id.*

37. Alicia T.F. Bazzano et al., *Off-Label Prescribing to Children in the United States Outpatient Setting*, 9 ACAD. PEDIATRICS 81, 83 (2009).

38. Corrado Barbui et al., *Off-Label and Non-Classical Prescriptions of Antipsychotic Agents in Ordinary In-Patient Practice*, 109 ACTA PSYCHIATRICA SCANDINAVICA 275, 277 (2004); Stephen

label drug use among cancer specialists, the General Accounting Office found in 1989 that one-third of the drugs prescribed were used off-label.³⁹ Furthermore, more than half of all cancer patients are prescribed with a drug off-label.⁴⁰

Overall, off-label drug use is a common component of medical care. As Beck and Azari conclude:

The bare fact of off-label use of a device or drug carries with it no medical information, either express or implied. While patients might have some assurance that uses actually appearing on a label are safe and effective, they cannot imply from a label's silence that a particular use recommended by their physician is unsafe, risky, novel or untried.⁴¹

The extensive use of pharmaceuticals off-label could raise the legal issue of whether physicians need to obtain the informed consent of their patients when prescribing a drug for an off-label use. Currently, physicians are required to provide their patients with certain relevant information. This includes the nature of the ailment, a description of the proposed treatment and alternatives, the probability of success for the proposed therapy and alternatives, and the risks to the patient.⁴² However, patients do not need to be informed that a prescribed drug is being used in an off-label manner, but only if a new use is being formally tested as part of a research protocol.⁴³

Overall, we observe that pharmaceuticals are frequently used for non-approved or off-label indications, and also that such use carries no medical information. Off-label use is a common form of medical practice in many specialties⁴⁴ and as the FDA does not assume supervisory control over the practice, nor does it proscribe such use.⁴⁵ This feature of pharmaceutical usage sets the framework for the recent spate of FDA regulations and legal decisions.

Kogut et al., *Prescribing of Antipsychotic Medication in a Medicaid Population: Use of Polytherapy and Off-Label Dosages*, 11 J. MANAGED CARE PHARMACY 17 (2005); Elisabeth Weiss et al., *Off-Label Use of Antipsychotic Drugs*, 20 J. CLINICAL PSYCHOL. 695 (2000).

39. U.S. GEN. ACCOUNTING OFFICE, *PRESCRIPTION DRUGS: IMPLICATIONS OF DRUG LABELING AND OFF-LABEL USE: STATEMENT OF SARAH F. JAGGER 2-3* (1996).

40. *Id.* at 3.

41. Beck & Azari, *supra* note 33, at 89.

42. Largent et al., *supra* note 22, at 1746.

43. Beck & Azari, *supra* note 33, at 85.

44. *See supra* notes 33-40 and accompanying text.

45. *See supra* notes 31-32 and accompanying text.

III. THE LAW AND REGULATION OF ADVERTISING AND PROMOTION

In contrast to the FDA's restrained approach toward physician prescribing of pharmaceuticals, the agency has taken a strong stand against off-label promotional activities. When off-label prescribing first became an important issue in the 1980s, then Commissioner David Kessler specifically decided that the FDA's response would be directed at drug companies rather than prescribers and that the agency's efforts would be aimed principally at discouraging unauthorized promotional efforts.⁴⁶ The FDA originally took the position that any claim that a drug could be "safe and effective" for an off-label use was always "false or misleading," although more recently it retreated from that strong position.⁴⁷ Notably, it was Kessler's decision that led to the FDA's current regulatory posture to acknowledge and accept off-label sales of pharmaceuticals while at the same time prohibiting all efforts by suppliers to provide any information, whether through advertising or representatives, on how their products should be used.

To be sure, the FDA has created a pathway through which additional indications could be approved, added to the drug's label, and then promoted. Companies can file Supplemental New Drug Applications (sNDAs) following an earlier approval for the purpose of adding additional indications. Between 2000 and 2006, there were 294 sNDAs filed for this purpose, although that number was only about two percent of the nearly 14,000 sNDAs filed for all purposes during the same years.⁴⁸ Whatever the advantages associated with adding additional indications to the drug's label, they were apparently exceeded in most cases by the costs and risks involved.

With this pathway largely blocked by economic if not regulatory factors, manufacturers faced the question of what practices to follow in marketing their drugs. A critical question was whether they could legally provide any information to physicians on non-indicated uses of their drugs. Prior to the FDA Modernization Act of 1997, the FDA answer was no.⁴⁹ However, FDA restrictions came under sharp attack from the American Medical Association (AMA) in the 1990s, with AMA representatives calling for the FDA to permit physicians more access to

46. CARPENTER, *supra* note 25, at 619.

47. *Id.* at 618, 620–21; *see also* Jerry Avorn et al., *Forbidden and Permitted Statements about Medications — Loosening the Rules*, 373 N. ENG. J. MED. 967 (2015).

48. CARPENTER, *supra* note 25, at 613.

49. Avorn et al., *supra* note 47, at 967–68.

information on off-label uses by allowing manufacturers to distribute scientific studies about such uses.⁵⁰ Congress responded with the Modernization Act of 1997, which authorized manufacturers to distribute unabridged peer reviewed publications or reference materials to health care practitioners, pharmacy benefit managers, health insurers, group health plans, and federal and state governments.⁵¹ In its implementation of the new law, the FDA required these distributed materials to disclose the manufacturer as the source of the materials and to indicate specifically that the FDA had not approved the information.⁵² The effect of these changes was to allow for the broader distribution of research relevant to off-label use but not for the systematic collection of this information.

An early legal challenge to the FDA's regulatory efforts came in *Washington Legal Foundation v. Henney*⁵³ in 1998. The question to be decided was whether the FDA was regulating speech or conduct, where the latter was permissible but not the former.⁵⁴ The trial judge responded strongly; he interpreted the prohibition as regulating speech and enjoined the FDA's actions.⁵⁵ However, on appeal, the injunction was vacated in part, although it was unclear as to what then remained of the FDA's prohibitions.⁵⁶ While direct marketing of off-label indications remained prohibited, the door was now open for drug companies to disseminate bona fide scientific information.

This regulatory ambivalence left drug manufacturers with uncertain guidelines on how to promote off-label sales of their existing products. Some companies created separate offices from their regular marketing staff to provide information on off-label indications.⁵⁷ In many cases, the FDA found the adopted approaches inconsistent with FDA guidelines and companies were subject to substantial penalties for off-label marketing activities⁵⁸:

50. Beck & Azari, *supra* note 33, at 103.

51. *Id.*

52. Food and Drug Administration Modernization Act of 1997, 21 U.S.C. §§ 360aa, 551 (2012); Robert I. Field, *The FDA's New Guidance for Off-Label Promotion Is Only a Start*, 33 HEALTH CARE & L. 220, 249 (2008).

53. 202 F.3d 331 (D.C. Cir. 2000).

54. *Id.* at 331.

55. *Id.* at 335.

56. *Id.* at 333–37.

57. Scott Whitcup, Chief Scientific Officer, Allergan, Inc., *The Medicine, Law and Economics of Botox* (Feb. 5, 2015).

58. W. Kip Viscusi & Richard J. Zeckhauser, *Regulating Ambiguous Risks: The Less than Rational Regulation of Pharmaceuticals* 6–7 (Harv. Kennedy Sch., Faculty Research Working

Company	Relevant Drug	Year	Penalty (millions)
AstraZenica	<i>Seroquil</i>	2010	\$520 USD
Novartis	six drugs	2010	\$423 USD
Amgen	<i>Aranesp</i>	2012	\$762 USD
J&J	<i>Ripersdal</i>	2012	\$181 USD

The legal environment shifted again with the *Caronia* decision of 2012,⁵⁹ which in turn rested on *Sorrell v. IMS Health, Inc.*,⁶⁰ a United States Supreme Court decision from the year before.⁶¹ In the earlier decision, the Court ruled by a six to three margin that “speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.”⁶² In reaching this decision, the Court specifically rejected the dissenting position that this form of speech “is inextricably related to a lawful governmental effort to regulate commercial enterprise.”⁶³ Critically, the *Sorrell* decision was law when the *Caronia* matter reached the appellate court.

The case against Alfred Caronia was tried in 2009, years before the Supreme Court’s decision in *Sorrell*. Caronia had been convicted of the misdemeanor of promoting the off-label use of one of his employer’s pharmaceuticals and was subject to one year of probation, a fine of twenty-five dollars together with one hundred hours of community service.⁶⁴ An interesting feature of the case is that it arose from a government sting operation in which Caronia had been contacted by an informant and asked specifically for information on the off-label uses of a drug he was promoting. He complied with the request, and the conviction followed.⁶⁵

Caronia appealed his conviction, and in December 2012, a three judge panel of the Second Circuit overturned his conviction. By a two to one vote, the panel found “that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA

Paper Series, Working Paper No. 14-005, 2015).

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

60. 131 S. Ct. 2653 (2011).

61. *Id.*

62. *Id.* at 2659.

63. *Id.* at 2673.

64. *Caronia*, 703 F.3d at 159, 160.

65. Michael A. Walsh, *The First Amendment and the Emerging Tort of Off-Label “Promotion”* 18–23 (Wash. Legal. Found.: Critical Legal Issues Working Paper Series, Working Paper No. 183, 2013).

for speech promoting the lawful, off-label use of an FDA-approved drug.”⁶⁶ Although the majority sought to limit the decision’s reach, the dissenting judge warned otherwise. She observed that “the majority calls into question the very foundations of our century-old system of drug regulation.”⁶⁷

The *Caronia* decision emphasized that “while the FDCA makes it a crime to misbrand . . . a drug, the statute and its accompanying regulations do not expressly prohibit or criminalize off-label promotion.”⁶⁸ Instead, this prohibition is an FDA enforcement practice and not the law itself. *Caronia*’s conviction, the court emphasized, was based on his “promoting and marketing the off-label use of . . . an FDA-approved drug,”⁶⁹ and not directly of “misbranding.” In so doing, the court sought “to avoid a serious constitutional question” of whether the statute’s criminalization of misbranding was itself a violation of the First Amendment.⁷⁰

What the *Caronia* decision left unanswered was the evident conflict between “prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use” of the company’s products.⁷¹ It suggested, moreover, that “such barriers to information about off-label use could inhibit, to the public’s detriment, informed and intelligent treatment decisions.”⁷²

Finally, the court drew the following conclusion:

If the government’s objective is to shepherd physicians to prescribe drugs only on-label, criminalizing manufacturer promotion of off-label use while permitting others to promote such use to physicians is an indirect and questionably effective means to achieve that goal. . . . Accordingly, the government’s prohibition of off-label promotion by pharmaceutical manufacturers “provides only . . . remote support for the government’s purpose.”⁷³

Not only did the court find that prohibition in question violated the First Amendment, but that it also served little regulatory purpose.⁷⁴ The

66. *Caronia*, 703 F.3d at 169.

67. *Id.*

68. *Id.* at 160.

69. *Id.* at 161.

70. *Id.* at 162.

71. *Id.* at 179.

72. *Id.* at 166.

73. *Id.* at 167.

74. *Id.* at 167, 169.

prosecution did not seek either an *en banc* review of the decision or an appeal to a higher court.⁷⁵

The *Caronia* decision was modified slightly in an appellate decision in the *United States v. Harkonen*⁷⁶ case filed the following year, in 2013.⁷⁷ In that case, the defendant had issued a press release touting a drug's off-label use in language judged fraudulent even if not literally false.⁷⁸ Emphasizing that the First Amendment does not protect fraudulent speech, the court upheld the conviction.⁷⁹ In this case, the prosecution skirted the issue of off-label marketing by emphasizing the misleading means that were used.⁸⁰ The decision thus avoided the essential question of whether manufacturers are permitted to promote through truthful means the off-label indications of their products.

More recently, a successor suit was filed in the Second Circuit, where *Caronia* remains a valid precedent, seeking to enjoin the FDA from enforcing its prohibition of the truthful promotion of off-label indications.⁸¹ The FDA responded indignantly and argued that the suit was “a frontal assault . . . on the framework of new drug approval that

75. Thomas M. Burton, *FDA Won't Appeal Free-Speech Marketing Decision*, WALL ST. J. (Jan. 23, 2013), <http://www.wsj.com/articles/SB10001424127887324539304578260323575925896> [<https://perma.cc/9YB6-XMRZ>].

76. 510 F. App'x 633 (9th Cir. 2013).

77. *Id.*

78. The drug involved was Actimmune, which had been approved for two rare disorders primarily affecting children. *Harkonen v. U.S. Dep't of Justice*, No. 4:12-cv-00629-CW, 2012 WL 6019571, at *4 (N.D. Cal. Dec. 3, 2012), *aff'd*, 800 F.3d 1143 (9th Cir. 2015). The company began a Phase III trial of the drug for Idiopathic Pulmonary Fibrosis (IPF), a usually fatal lung disease affecting adults. *Id.* The overall effects of the Phase III trial failed to show that the drug was effective for treating IPF. *Id.* After the trial, the company conducted additional analyses not originally part of the trial and found that the drug appeared to be effective in patients with mild to moderate IPF—that is, the results in this group were statistically significantly different than in the control group. *Id.* FDA staff told the company that this trial data would not be sufficient to gain approval for Actimmune as a treatment for IPF and that further clinical testing would be required. *Id.* On the day after receiving that advice, the company issued a press release stating “preliminary data from its Phase III clinical trial of Actimmune® (Interferon gamma-1b) injection for the treatment of idiopathic pulmonary fibrosis (IPF), a debilitating and usually fatal disease for which there are no effective treatment options, demonstrate a significant survival benefit in patients with mild to moderate disease randomly assigned to Actimmune versus control treatment (p = 0.004)” and also claimed the trial showed “a statistically significant survival benefit in patients with mild to moderate IPF.” *Id.* at *4–5. The government complaint asserted that the press release falsely portrayed the clinical trial as having established that the drug reduced mortality. *Id.* at *5.

79. *Harkonen*, 510 F. App'x at 636, 637.

80. Brief for the Plaintiff-Appellee at 52–59, *Harkonen*, 510 F. App'x 633 (Nos. 11–10209, 11–10242).

81. *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, No. 1:15-cv-03588-PAE, 2015 WL 4720039, at *17 (S.D.N.Y. Aug. 7, 2015).

Congress created in 1962.”⁸² In doing so, the agency maintained that the *Caronia* decision was limited to the facts of that particular case and did not apply more broadly.⁸³

The court disagreed and rejected the FDA’s position. It ruled that “the First Amendment . . . holds protected, and outside the reach of the FDCA’s misbranding provisions, off-label promotion . . . where it wholly consists of truthful and non-misleading speech.”⁸⁴ However, the court found two limits to the *Caronia* ruling: “[f]irst the First Amendment does not protect false or misleading commercial speech. . . . [And] [s]econd, the First Amendment protects expression, not conduct.”⁸⁵

Until the Supreme Court has the opportunity to rule on these issues, they remain in conflict. The *Caronia* decision is controlling precedent in only the three states of the Second Circuit. In forty-seven states, the FDA retains its authority to prohibit the marketing and promotion of off-label indications. However, the agency is evidently concerned by the prospect that the Supreme Court would limit its regulatory authority if the question of off-label promotion ever came before it.⁸⁶ While the FDA can evade that decision for a while, it probably cannot do so indefinitely.⁸⁷ Suppose that the Supreme Court rules that the First Amendment takes priority over the FDA’s regulatory authority, what might we then expect of the current structure of pharmaceutical regulation? We return to this question in our closing discussion of policy judgments.⁸⁸

IV. THE ECONOMICS OF OFF-LABEL PRESCRIBING

The widespread pattern of off-label prescribing follows directly from the physician’s decision-making. A physician evaluating a specific

82. *Id.* at *35.

83. *Id.* at *17 n.34.

84. *Id.* at *52.

85. *Id.*

86. This is one interpretation of the decision not to appeal *Caronia*, discussed *supra* notes 74–75 and accompanying text.

87. In *United States v. Vascular Solutions, Inc.*, the U.S. Attorney included the following statement in his proposed jury instructions: “[i]t is also not a crime for a device company or its representatives to give doctors wholly truthful and non-misleading information about the unapproved use of a device.” Proposed Jury Instructions at 31, *United States v. Vascular Sols., Inc.*, No. 5:14-cr-00926-RCL (W.D. Tex. filed Jan. 7, 2016). He cites both the *Caronia* and *Amarin Pharma* decisions noted here for this statement even though they were decided in a different circuit. *Id.* at n.26.

88. *Infra* notes 125–40 and accompanying text.

patient must assess whether the benefits from a drug outweigh both its direct costs and the potential complications and side effects for the patient. The benefits, potential complications, and side effects will be known only imprecisely, because even effective drugs may not work for a specific patient and patients differ in their risk and susceptibility to complications and side effects. Thus for a specific patient being treated, the physician must assess the likely benefit and likely risk of complications. For on-label use, the physician can assume that for the average patient for whom the drug is indicated, the clinical trial data indicated that the benefits would exceed their costs, or the drug would not have been approved for that use. But where do physicians obtain comparable information for off-label uses? Or, to put the question another way, how do physicians make the decisions about risk and benefit to inform their practice?

As noted earlier, there are two alternate routes toward gaining information on a pharmaceutical's attributes. What is apparent is that both are relevant for physician decision-making and that prescribing outcomes depend on more than the clinical trials required by the FDA.

While the previous discussion explored the physician's prescribing decisions, we now consider the decisions of drug manufacturers on whether to sponsor additional clinical trials and then seek an sNDA for an additional on-label indication. We consider the economic implications of the FDA's regulations in a setting where off-label sales can be substantial.

For a drug with only a single indication, that question does not arise. That indication is the subject of the firm's NDA, which must be approved before the product can be sold.⁸⁹ Where the drug has a second indication, however, the firm's decision process is more nuanced. It recognizes that unauthorized marketing entails legal risks and the possibility of both large fines and legal judgments. Moreover, even if the firm does not engage in unauthorized marketing efforts, there can be strong prospects for making substantial off-label sales.

On the other side of the ledger, the manufacturer can decide to file an sNDA specifically to gain approval for this second indication. Even though Phase I clinical trials are not indication-specific and therefore have already been carried out, this is not the case for Phase II and III trials that relate to specific indications.⁹⁰ And these additional trials can be quite costly.

89. *See supra* Part I.

90. *Id.*

A recent study surveyed out-of-pocket costs for investigational compounds, which are of course heavily weighted to first indications. In 2013 dollars, these costs averaged \$58.6 million for Phase II and \$255.4 million for Phase III trials.⁹¹ In effect, these figures indicate the prospective cost of securing marketing authorization for a second indication. Furthermore, there is no guarantee that these trials will be successful. Currently nearly forty-four percent of Phase II trials fail; and even more than ten percent fail for Phase III trials.⁹² Investing in additional clinical trials, as required to authorize a second indication, is both costly and risky.

There is another issue as well. Even without benefit of on-label status, many drugs still gain considerable standing with prescribing physicians, which can lead to substantial sales. While those sales may be enhanced by a successful set of clinical trials, they can also be dampened by unsuccessful trials. If knowledge of unsuccessful trials becomes widespread, there is even the possibility that current off-label sales would decline substantially. Putting all these considerations together, we would not be surprised to find little appetite among drug manufacturers for securing additional approved indications.

These considerations can be summarized through the following model, which describes the additional profits projected for a drug manufacturer from engaging in the clinical trials required to secure a second approved indication. Its expected profits from doing so are then:

$$\Delta \Pi = p (\Delta S1) + (1 - p) (\Delta S2) + (X - C)$$

In this equation,

$\Delta \Pi$ represents the greater profits from doing a second trial;

p is the probability of a successful second trial;

$\Delta S1$ is the increased sales from a successful second trial;

$\Delta S2$ is the reduced sales resulting from an unsuccessful second trial;

X are the savings from avoiding liability for off-label marketing; and

C represents the cost of the second trial.

This model assumes a given level of profits from current on-label and

91. Joseph A. DiMasi, Dir., Econ. Analysis, Tufts Ctr. for the Study of Drug Dev., Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs (Dec. 3, 2015) (on file with *Washington Law Review*).

92. *Id.*

off-label prescribing and also an anticipated level of risk from the liability associated with off-label use. In this equation, we ignore any costs associated with producing the product.

As anticipated, as the expected value of p increases, the firm finds it increasingly beneficial to carry out the second trial. In the limit, when $p = 1$, so that a successful test is assured, it is then profitable to undertake the second trial so long as:

$$\Delta S1 > C - X$$

This expression indicates the critical importance for these decisions of the level of C —the cost of the second trial—which can be quite high.

In addition to the marginal calculations facing the firm under current FDA rules, there is a second relevant margin as well. This second margin refers to an alternate policy regime under which current FDA rules against off-label marketing are withdrawn. Consider the following structure where there are four possible outcomes:

1. Under current rules, the manufacturer would have carried out a successful second trial but does not do so when the requirements are withdrawn;
2. Under current rules, the manufacturer would have carried out an unsuccessful second trial but does not do so when the requirements are withdrawn;
3. The manufacturer would not have carried out a second trial, but had it done so, the trial would have been successful;
4. The manufacturer would not have carried out a second trial, but had it done so, the trial would have been unsuccessful.

These four alternatives describe the alternate outcomes possible if the current FDA rules are withdrawn. We consider the welfare implications of each of them.

Cases 1 and 3 have similar implications for welfare calculations in that only positive outcomes follow from the revised policy posture. In Case 1, the market outcomes are the same as under the original FDA rules, although without the costly trials, so their costs are saved. In Case 3, the trials are not carried out in any case, but now marketing the second indication is permitted. Presumably, sales are increased and greater health benefits achieved from the increased use of effective drugs. Although the sources of the gains are different in the two cases, they are both fully positive.

Case 2 offers a more uncertain outcome. Clinical trials, which would

have been undertaken under current FDA rules but which would not have been successful, are now foregone and their cost saved. However, an inefficacious drug can now be promoted and its sales are increased as a result. That case may represent the most idealized circumstances supporting the existing rules. However, the net effect is uncertain because the cost of the trials must be balanced against the health benefits derived from limiting sales of an inefficacious product. The issue turns on the relative size of the resulting health benefits as compared with the costs of the trials.

In Case 4, the trials are not undertaken in any event so there are no cost savings from dropping the current FDA rules. However, companies are now permitted to promote inefficacious drugs leading presumably to increased sales without commensurate health effects. Preventing the marketing and promotion of such drugs is the ostensible purpose behind the current FDA rules, and these are no longer operative. There are only negative effects from eliminating the current FDA rules in this case.

Although the health outcomes of the four cases are reasonably apparent, at least in general terms, what is unclear are the probabilities associated with each alternative. Appraising the policy gains or losses resulting from eliminating the current FDA rules requires a judgment of the relative frequency of the four alternatives; but unfortunately there is not sufficient information available to make that judgment.

V. THE MEDICINE OF OFF-LABEL PRESCRIBING

The medical rationale for off-label use seems clear. While clinical trials estimate average effects, one of the hallmarks of drug therapies is the heterogeneity of patient outcomes,⁹³ which has been especially noted in regard to psychotropics.⁹⁴ Physicians need to tailor their choices of therapy to the responsiveness of their patients. This factor is particularly relevant where evidence from clinical trials is limited. For example, children are often excluded from trials because the number of cases is small and the gains to the drug company of having the drug licensed for children are more limited. But observation and understanding of a drug's underlying mechanism of action can strongly suggest its extension to treatment of children. Furthermore, there can be similar reasons to

93. See generally David J. Stewart & Razelle Kurzrock, *Fool's Gold, Lost Treasures, and the Randomized Clinical Trial*, 13 BMC CANCER 193 (2013).

94. See generally Stephen Z. Levine & Stefan Leucht, *Treatment Response Heterogeneity in the Predominant Negative Symptoms of Schizophrenia: Analysis of Amisulpride vs Placebo in Three Clinical Trials*, 156 SCHIZOPHRENIA RES. 107 (2014).

extend a drug's application beyond the conditions for which it is indicated on the drug's label.⁹⁵

In prescribing drugs for off-label indications, physicians employ both their own direct experience and that of other physicians as reported on a case by case basis. Case reports are common in clinical journals, and often serve to indicate what care is appropriate. The exploration of clinical effectiveness for individual patients has received increased attention as representing "N-of-1" trials, and there are available guidelines for conducting and reporting these trials.⁹⁶ If there is sufficient interest in a potential use, a post-licensing clinical trial may also be pursued, but this is not often necessary to establish an off-label use as standard practice.

Moving beyond the experience of an individual physician's practice requires physicians to rely on case reports and trials of varying sophistication and rigor as reported in the medical literature. Acceptable off-label prescribing is often reflected in published drug compendia offering recommendations on appropriate use,⁹⁷ local or professional society practice guidelines, and payer reimbursement policies which are based on compendia, professional society recommendations, and physicians' own assessment of appropriateness.

There are many examples of how drugs have become widely used for off-label indications through such means, and we discuss here two as illustrative of the process.

Persistent pulmonary hypertension (PPHN) in the newborn is a serious condition related to a failure in the normal transition in circulation from low fetal pulmonary blood flow to a high pulmonary flow as the lungs assume the function of exchanging oxygen and carbon dioxide.⁹⁸ The causes are diverse and untreated mortality is high.⁹⁹

Inhaled nitrous oxide, which acts as a pulmonary vasodilating agent, has emerged as the preferred standard treatment, although up to thirty percent of patients do not respond to it.¹⁰⁰ Viagra (sildenafil) is also a

95. Jeffrey L. Blumer, *Off-Label Uses of Drugs in Children*, 104 PEDIATRICS 598, 599 (1999).

96. See generally Larissa Shamseer et al., *CONSORT Extension for Reporting N-of-1 Trials (CENT) 2015: Explanation and Elaboration*, 350 BMJ 1793 (2015); Sunita Vohra et al., *CONSORT Extension for Reporting N-of-1 Trials (CENT) 2015 Statement*, 350 BMJ 1738 (2015).

97. See generally Brown, *supra* note 18.

98. Steven H. Abman et al., *Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society*, 132 CIRCULATION 2037, 2038 (2015).

99. *Id.* at 2038–39.

100. J.N. Travadi & S.K. Patole, *Phosphodiesterase Inhibitors for Persistent Pulmonary Hypertension of the Newborn: A Review*, 36 PEDIATRIC PULMONOLOGY 529, 529–35 (2003).

vasodilating agent. In 1999, a case was reported in U.S. medical literature of Viagra use to assist in the withdrawal of an infant from inhaled nitrous oxide therapy.¹⁰¹ Following this report, several cases described the successful use of Viagra in babies in Bangladesh and India to treat pulmonary hypertension in children when standard therapy had failed.¹⁰²

There was considerable controversy regarding this therapy, including charges that it might encourage unethical experimentation. A 2003 review article concluded that “recent studies have suggested a role for specific phosphodiesterase (PDE) inhibitors in the management of PPHN [and] Sildenafil [Viagra] appears the most promising of such agents.”¹⁰³ The review emphasized, however, the “need for randomized-controlled trials to determine the safety, efficacy, and long-term outcome following treatment with sildenafil in PPHN.”¹⁰⁴ Over the next four years, additional case reports on the use of Viagra in the treatment of neonatal pulmonary hypertension were published¹⁰⁵ as well as reports of animal models¹⁰⁶ and a small-scale randomized trial¹⁰⁷ with mixed

101. Andrew M. Atz & David L. Wessel, *Sildenafil Ameliorates Effects of Inhaled Nitric Oxide Withdrawal*, 91 ANESTHESIOLOGY 307, 307–09 (1999).

102. See generally D. Abrams et al., *Sildenafil as a Selective Pulmonary Vasodilator in Childhood Primary Pulmonary Hypertension*, 84 HEART E4 (2000); Sanjay Kumar, *Indian Doctor in Protest After Using Viagra to Save “Blue Babies,”* 325 BMJ 181 (2002); James Oliver & David J. Webb, *Sildenafil for “Blue Babies”: Such Unlicensed Drug Use Might Be Justified as Last Resort*, 325 BMJ 1174 (2002).

103. Travadi & Patole, *supra* note 100, at 529.

104. *Id.*

105. See generally M. Chaudhari et al., *Sildenafil in Neonatal Pulmonary Hypertension Due to Impaired Alveolarisation and Plexiform Pulmonary Arteriopathy*, 90 ARCHIVES DISEASE CHILDHOOD: FETAL & NEONATAL ED. F527 (2005); Kam-lun Ellis Hon et al., *Oral Sildenafil for Treatment of Severe Pulmonary Hypertension in an Infant*, 88 BIOLOGY NEONATE 109 (2005); Robert L. Keller et al., *Treatment of Rebound and Chronic Pulmonary Hypertension with Oral Sildenafil in an Infant with Congenital Diaphragmatic Hernia*, 5 PEDIATRIC CRITICAL CARE MED. 184 (2004); Astrid E. Lammers et al., *Intravenous Sildenafil as an Effective Treatment of Pulmonary Hypertensive Crises During Acute Intestinal Malabsorption*, 16 CARDIOLOGY YOUNG 84 (2006); E. Garcia Martinez et al., *Sildenafil en el Tratamiento de la Hipertensión Pulmonar [Sildenafil in the Treatment of Pulmonary Hypertension]*, 59 ANALES DE PEDIATRÍA 110, 110 (2003) (see abstract); J.A. McEniery et al., *Infant Pertussis Deaths and the Management of Cardiovascular Compromise*, 40 J. PEDIATRIC CHILD HEALTH 230 (2004).

106. See generally Karen E. Binns-Loveman et al., *Sildenafil and an Early Stage of Chronic Hypoxia-Induced Pulmonary Hypertension in Newborn Piglets*, 40 PEDIATRIC PULMONOLOGY 72 (2005); Yvonne A. Bremer et al., *Sildenafil Citrate (Viagra) Induces Cardioprotective Effects After Ischemia/Reperfusion Injury in Infant Rabbits*, 57 PEDIATRIC RES. 22 (2005); Philippe Deruelle et al., *Pulmonary Vascular Effects of Nitric Oxide-cGMP Augmentation in a Model of Chronic Pulmonary Hypertension in Fetal and Neonatal Sheep*, 289 AM. J. PHYSIOLOGY: LUNG CELLULAR & MOLECULAR PHYSIOLOGY, at L798 (2005); Philippe Deruelle et al., *Effects of BAY 41–2272, a Soluble Guanylate Cyclase Activator, on Pulmonary Vascular Reactivity in the Ovine Fetus*, 289

results. The use of Viagra to treat neonatal pulmonary hypertension is increasing and becoming more established in clinical practice despite calls for both clinical trials and the characterization of this treatment modality as experimental.

The need for follow-up clinical trials for off-label practices, which had been established originally through case reports and a growing consensus among practitioners, is also illustrated by the case of Aprotinin. That drug is approved “for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion.”¹⁰⁸ This drug became a standard treatment to reduce the risk of bleeding for patients undergoing invasive cardiovascular procedures even though it had not been subject to widespread testing. An observational study, however, reported that use of Aprotinin was associated with twice the risk of renal failure requiring dialysis.¹⁰⁹ The drug’s sales were suspended in May 2008, but sales resumed in Europe in 2012 after the European Medicine Agency recommended the suspension be lifted.¹¹⁰

These two cases illustrate several important themes in evaluating the medical implications of the off-label drug use. First, as noted earlier, the methods and assumptions of the clinical trials used initially to justify the licensure of drugs, and those used to extend their uses to other indications, are substantially different and have never been reconciled. Moreover, we do not offer here a means to integrate these two kinds of knowledge or understanding. This is the case despite the considerable interest in developing methods for individualizing therapy based on genetic, metabolic, or physiological markers.

Second, the case of Aprotinin illustrates that even where there is close observation of individual cases, there remains a need for larger-scale pooling and systematic review of the reported body of cases to fully understand the off-label use of particular drugs. A commentary in the

AM. J. PHYSIOLOGY: LUNG CELLULAR & MOLECULAR PHYSIOLOGY, at L727 (2005).

107. See generally Christian Stocker et al., *Intravenous Sildenafil and Inhaled Nitric Oxide: A Randomised Trial in Infants After Cardiac Surgery*, 29 INTENSIVE CARE MED. 1996 (2003).

108. TRASYFOL® (APROTININ INJECTION), FDA.GOV (2006), http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020304s022lbl.pdf [<https://perma.cc/UZT7-W8J3>].

109. Dennis T. Mangano et al., *The Risk Associated with Aprotinin in Cardiac Surgery*, 354 NEW ENG. J. MED. 353, 353 (2006).

110. *Aprotinin Injection (marketed as Trasyol) Information*, FDA.GOV (last updated May 14, 2008), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142720.htm> [<https://perma.cc/W7K5-4569>].

same issue in which the Aprotinin result was reported argued for the development of improved statistical and epidemiological methods to minimize the confounding of observational studies.¹¹¹ Among the approaches recommended was the use of propensity scoring and collection of substantial number of covariates.¹¹² The author noted the need for obtaining results that can be treated with confidence and distinguished them from methods that require a substantial number of cases and substantial data on each case.¹¹³ A further statement in the same issue called for more extensive Phase IV clinical trials—that is, post-approval trials—to “be required before the indications for pharmaceutical agents are expanded, particularly when increased doses are required or administration in high-risk patients is proposed” and that the FDA should encourage and support such trials.¹¹⁴

A commentary on published studies reported that the off-label use of Misoprostol to induce labor had contributed to uterine rupture. It concluded that “[t]he off-label use of drugs should be limited to officially sanctioned, carefully controlled trials. Opportunistic off-label drug use, with no mechanism to guarantee adequate evidence, again and again has had tragic consequences for women and children.”¹¹⁵

Physicians and insurers seeking guidance on appropriate off-label use have various sources of information beyond the pharmaceutical companies, of which drug compendia are a major one. The Medicare program, for example, restricts reimbursement for prescription drugs to “medically accepted indications.”¹¹⁶ This is defined as on-label FDA-

111. See generally David Hunter, *First, Gather the Data*, 354 NEW ENG. J. MED. 329 (2006).

112. Hunter describes the propensity scoring in the following language:

For instance, the propensity-score approach estimates the probability that a person will be given a prescription for a particular drug on the basis of his or her demographic, lifestyle, and clinical characteristics; this score can then be used to control for potential confounding from these characteristics. Another potential application of the score is to match patients who received the study drug with control patients who did not but who have the same propensity score; in essence, this is an attempt to replicate the process of randomization, in which other unmeasured and potentially confounding characteristics are randomly distributed among those who receive a drug and those who do not.

Id. at 330.

113. *Id.*

114. Gus J. Vlahakes, *The Value of Phase 4 Clinical Testing*, 354 NEW ENG. J. MED. 413, 414 (2006).

115. Marsden Wagner, *Off-Label Use of Misoprostol in Obstetrics: A Cautionary Tale*, 112 BJOG 266, 267 (2005).

116. See U.S. CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL: CHAPTER 6 – PART D DRUGS AND FORMULARY REQUIREMENTS § 10.6 (2010) <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/chapter6.pdf> [https://perma.cc/37W9-V6CV].

approved use or use supported by one or more compendia identified by statute.¹¹⁷ These compendia are the American Hospital Formulary Service Drug Information (AHFS-DI), the United States Pharmacopeia-Drug Information publication, and the DrugDEX Information System. Other compendia also exist. Because the compendia are an authoritative source of information on acceptable off-label uses, drug companies have substantial interest in seeing their products included in them.

Compendia use similar methods for reviewing drugs and uses for inclusion:

A team of researchers (who may be compendia employees) reviews the literature for new clinical trials presented in papers, meeting abstracts, guidelines, or review articles. The editorial team evaluates sources of new data, ideally using an explicit and uniform set of standards. A decision is made about whether to include the new results in the updated chapter. Depending on the particular compendium publisher, this decision may involve the use of external consultants.

Once a draft is prepared, most compendium publishers ask external reviewers (often consultants) to review the draft. The editors subsequently decide how, and whether, to incorporate the reviewers' comments. A final draft is then prepared, approved, and published.¹¹⁸

Despite their similar processes, compendia do not always reach similar conclusions. There is extensive literature reporting conflicts in the compendia across appropriate uses and flagging of issues such as drug-drug interactions.¹¹⁹

The authors of a Duke white paper on this subject conclude that the sources of information for assessing off-label use can be weak and the potential for conflict of interest in the review of indications can be high, with different compendia approaching the conflict of interest issue in a

117. *Id.*

118. MCKINNEY ET AL., *supra* note 20, at 27–28.

119. See generally Amy P. Abernethy et al., *Systematic Review: Reliability of Compendia Methods for Off-Label Oncology Indications*, 150 ANNALS INTERNAL MED. 336 (2009); D. Conde-Estevez et al., *Potential Clinical Relevant Drug-Drug Interactions: Comparison Between Different Compendia, Do We Have a Validated Method?*, 26 ANNALS ONCOLOGY 1272 (2015); Božana S. Nikolić & Maja S. Ilić, *Assessment of the Consistency Among Three Drug Compendia in Listing and Ranking of Drug-Drug Interactions*, 13 BOSNIAN J. BASIC MED. SCI. 253 (2013); Richard P. Paczynski et al., *Quality of Evidence in Drug Compendia Supporting Off-Label Use of Typical and Atypical Antipsychotic Medications*, 24 INT'L J. RISK & SAFETY MED. 137 (2012); Renee Twombly, *Drug Compendia in Oncology: Are They Flawed?*, 101 J. NAT'L CANCER INST. 1604 (2009).

variety of ways.¹²⁰ A 2014 assessment of compendia processes concluded, “[a]lthough the compendia publishers and CMS are aware of many of the current problems with the compendia and have attempted to improve the system, much more can and should be done.”¹²¹

It is not clear how much guidance physicians seek on off-label use or how rigorous their standards are for demonstrated effectiveness. A 2006 study by Radley found that among the twenty-one percent of drug prescriptions for off-label use “most (73%) lacked evidence of clinical efficacy, and less than one third (27%) were supported by strong scientific evidence.”¹²²

While the medical literature calls for expanded Phase IV trials, the sources of funding for such trials are not clear. One of the important lessons of current off-label use of drugs is that it limits the incentive for drug manufacturers to sponsor extended clinical trials of their drugs. Once a drug has been approved by the FDA, regardless of how narrow the basis for its approval, physicians can extend its use.¹²³ Prior to the FDA Modernization Act of 1997, drug companies faced substantial restrictions on distributing information on off-label use.¹²⁴ This may have created some incentive to formally sponsor trials. However, that changed with the relaxation of restrictions contained in the 1997 law.

Finally, we observe that the companies who develop the pharmaceuticals generally have considerable understanding of their attributes. As a result, seeking to exclude them from the information-gathering process can be an important factor which limits the drugs’ effective use.

CONCLUSION

The FDA offers conflicting judgments on the off-label use of approved pharmaceuticals. On the one hand, it is not dissuaded by the *Caronia* decision, and considers it largely a hurdle to be overcome. Since that decision is not binding in forty-seven states, the FDA still has room to make its rulings operative, although its reliance on U.S. attorneys and state attorneys general for its enforcement efforts may have some restraining influence.

120. See generally MCKINNEY ET AL., *supra* note 20.

121. Lindsey Gabrielsen, *Bias at the Gate?: The Pharmaceutical Industry’s Influence on the Federally Approved Drug Compendia*, 40 AM. J.L. & MED. 141, 163 (2014).

122. Radley et al., *supra* note 33, at 1023.

123. See *supra* Part II.

124. See *supra* Part II.

On the other hand, the FDA's own guidance advisories recognize the medical importance of much off-label pharmaceutical use. The agency states that "good medical practice . . . [may] require that physicians use legally available drugs, biologics and devices . . . for an indication not in the approved labeling."¹²⁵ While the agency cautions the prescribing physicians to base their use on "firm scientific rationale and on sound medical evidence," it further states that FDA permission for this use is not required.¹²⁶

In this pronouncement, the FDA's inconsistency is apparent. Although it suggests that off-label use should rest on strong medical evidence, it then restricts an important source from which that information can be gained. One reason for this contradiction could be that the agency believes any information received from a product's manufacturer, unlike that offered by other parties, can be biased and should not be trusted.

The agency's skepticism that manufacturers provide balanced and full information of the relevant evidence has some support. A 2011 review of forty-one unsealed whistleblower complaints found a wide range of unauthorized marketing mechanisms, including self-serving presentations of the medical literature in three-quarters of the cases and direct financial incentives for physicians in eighty-five percent of the cases.¹²⁷ While these observations are drawn from a limited sample of cases in which the FDA pursued fraud complaints, they offer a context for FDA concerns.

To an increasing extent, however, the FDA has lost its gate-keeping function. As pharmaceuticals are increasingly paid for by third-party payers, both private and public, the decisions of these parties on which drugs to support increasingly determines prescribing outcomes.¹²⁸ Unless payers are willing to authorize payment for particular drugs, physicians are wary of prescribing them—regardless of being legally permitted to do so. This leads to the question of whether payers will regularly authorize payment for off-label indications.

This question was the subject of a recent court challenge in *Layzer v.*

125. "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices - Information Sheet: Guidance for Institutional Review Boards and Clinical Investigators, FDA.GOV (June 25, 2014), <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm> [<https://perma.cc/K3QZ-QZLZ>].

126. *Id.*

127. Aaron S. Kesselheim et al., *Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, 8 PLOS MED., Apr. 2011, at 1, 1.

128. Shrank et al., *supra* note 21.

Leavitt,¹²⁹ which analyzed whether Medicare was obligated to pay for medications used for off-label indications.¹³⁰ By statute, Medicare is obligated to cover drugs used for a “medically accepted indication” as defined in certain compendia.¹³¹ In this case, the patient’s physician had ordered a drug with recognized support in the medical literature, although it was not for an approved indication included in the relevant compendia.¹³² Observing that “FDA-approved uses often lag behind knowledge of actual effective treatment,” the court dispensed with the compendia requirement and effectively authorized coverage.¹³³ The court ruled that, consistent with FDA’s published advisories, “medically accepted indications” can include off-label use.¹³⁴

In a related case, the district court was again asked to decide on Medicare’s coverage of non-label indications.¹³⁵ It ruled the program “does not cover ‘off-label’ . . . use that is not a ‘medically accepted indication.’”¹³⁶ However, it had previously limited the latter category to drugs either approved under the FDCA or authorized for inclusion in certain medical compendia.¹³⁷ There remains ambiguity as to what medical data is required for Medicare reimbursement.

Although the principal public payer’s reimbursement policies are embodied in statute, this is not so for private payers.¹³⁸ While guided by the terms of their contractual obligations, they have greater room to exercise judgment. They are also impacted by issues of cost and their judgment as to whether the drug’s therapeutic value is worth its cost. That judgment applies whether the relevant indication is on or off-label.

The critical missing feature in the FDA’s authority is cost. That factor is not part of its authorizing mandate. As costs increase and as payers rather than patients increasingly bear the costs of pharmaceutical interventions, the distinction between on- and off-label use could lose much of its significance. When payers rather than physicians or patients determine which drugs are paid for and for which purposes, and where

129. 770 F. Supp. 2d 579 (S.D.N.Y. 2011).

130. *Id.* at 581.

131. Wagner, *supra* note 115.

132. *Layzer*, 770 F. Supp. 2d at 582.

133. *Id.* at 586.

134. *Id.*

135. United States *ex rel.* Fox RX, Inc. v. Omnicare, Inc., No. 1:11-cv-00962-WSD, 2012 WL 8020674 (N.D. Ga. Aug. 29, 2012).

136. *Id.* at *8.

137. *Id.* at *18–19.

138. Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 391 (2009).

these decisions depend strongly on the payers' reading of the available medical literature, then there is little reason for keeping drug manufacturers from contributing to the ongoing debates. But this will happen only when and if the Supreme Court applies the *Caronia* rule generally throughout the country.

When patients paid for prescribed drugs out-of-pocket, as they did for nearly ninety-six percent of pharmaceuticals purchased in 1960,¹³⁹ then the prescribing decisions of physicians were critical, and the FDA's control over the relevant information available to physicians was controlling. However, as third-party payers have paid increasing proportions of the drug bill, they have asserted greater control over which drugs they will reimburse.¹⁴⁰ How payers make their decisions is still unclear, although it is reasonable to assume that insurers seek to maximize the therapeutic gain from the pharmaceuticals prescribed their subscribers for given levels of expenditures.

For payers, the distinction between on and off-label uses may become increasingly unimportant as compared with their own evaluation of the therapeutic gains resulting from the use of a pharmaceutical. In effect, payers can apply their own evaluations as contrasted with those embodied in the FDA's NDA. While this shift has been ongoing, it would likely be accelerated by a widespread acceptance of the *Caronia* rule. In effect, that regulatory change may be occurring just as its importance in the marketplace is declining. To the extent that payers become the gatekeepers for appropriate off-label use, how they make these decisions will be critical for patients and physicians. Specifically of concern will be how they assess evidence on appropriate use, the extent to which they rely upon the authoritative albeit flawed compendia, and the extent to which they ask pharmaceutical companies to provide additional information. The engagement of payers will introduce another set of external actors to which pharmaceutical companies will need to be responsive. That would be an ironic result of the widespread adoption of the *Caronia* rule.

139. Patricia M. Danzon & Mark V. Pauly, *Health Insurance and the Growth of Pharmaceutical Expenditures*, 45 J.L. & ECON. 587, 591 (2002).

140. Shrank et al., *supra* note 21.