

Drug Safety and Commercial Speech: Television Advertisements and Reprints on Off-Label Uses

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I. INTRODUCTION

The constitutional protections for commercial speech limit the ability of the U.S. Food and Drug Administration (FDA or Agency) to regulate the promotion of drugs in ways that have the potential to affect the public health. This paper examines the areas in which the constitutional protections have had a significant impact on the Agency's role, these being Direct-Consumer (DTC) television advertisements for prescription drugs and the distribution to doctors by a drug manufacturers of medical journal articles about an unapproved use for a drug. The commercial speech formula is geared toward restrictions on promotion of business activities and does not specifically deal with safety concerns.¹ Under the general test, though, disclosures about a safety risk can outweigh a governmental concern in preventing harm.

In *Thompson v. Western States Medical Center*,² the only Supreme Court case dealing with commercial speech protections for drugs, the Court recognized that preserving the integrity of the drug approval system was important to protect the public health, but it invalidated a restriction on advertising by pharmacies of the availability of prescription compounded drugs not approved by FDA. The Court found that a disclosure about unknown risks from the untested compound was the constitutionally preferred alternative to a restriction on advertising. The Court also believed it “questionable” without more proof that doctors would prescribe an unnecessary drug in response to a patient request prompted by an advertisement.³ Although compounded drugs are an obscure and limited category, the Court's rationale raises a constitutional question about the permissibility of a moratorium on DTC advertisements or other speech restrictions for drugs.

Justice Breyer, in dissent, maintained that a “more lenient application” of the Federal Constitution is needed, and warned against “an overly rigid ‘commercial speech’ doctrine” for governmental decisions that affect “health and safety.”⁴ Transforming these decisions into a constitutional one “would involve a tragic constitutional misunderstanding” as shown by the history in respect to the due process clause.⁵ Instead, for drugs, the test needs to be a “flexible” one that examines the restriction's “proportionality,

1. *Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557, 571 (1980) (invalidating a restriction on promotional advertisements aimed at increasing electric consumption).

2. 535 U.S. 357 (2002).

3. *Id.* at 374.

4. *Id.* at 389 (Breyer, J., dissenting).

5. *Id.*

the relation between restriction and objective, the fit between ends and means.”⁶ A safety-focused proportionality test would give safety risks more recognition.

This paper explores how a safety-focused proportionality test would apply to the areas in which commercial speech may limit FDA’s ability to restrict drug promotions on matters that bear on postapproval risks and off-label uses.⁷ The first issue examined is the constitutionality of a temporary ban or moratorium on DTC advertisements for newly approved drugs until more information is obtained about the safety risk. The premarket testing for drugs is limited in scope and cannot detect the full scope of risks that may occur when the drug is used for a longer period and by a large number of patients with more varied health conditions. The cardiovascular risks from Vioxx, a widely sold arthritis drug, found after the drug was on the market, created wide public concern about drug safety.⁸ A committee of the Institute of Medicine (IOM) of the National Academy of Science favored a moratorium while surveillance on postmarket risks was underway but recognized that there might be constitutional difficulties.⁹ Although many legal writers question the constitutionality of a blanket moratorium based on uncertainty,¹⁰ some believe it should be permissible¹¹ or favor a prereview to determine if a

6. *Id.* at 388.

7. This paper does not explore the extent to which the Agency would have authority for a moratorium under present law or the procedural measures that would be needed for a moratorium, important matters noted in COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., INST. MED. NAT’L ACAD. SCI., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* 169–70 (Alina Baciú et al. eds., 2007). See Part III.C for provisions on dispute resolution enacted when the law was amended to expand the Agency’s authority with respect to postapproval risk.

8. See *infra* Part III.

9. COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 171–72.

10. See Symposium, *Thoughts on Commercial Speech: A Roundtable Discussion*, 41 LOY. L.A. L. REV. 333, 347–48 (2007); see also *infra* Part IV.C.

11. See David C. Vladeck, *The Difficult Case of Direct-to-Consumer Drug Advertising*, 41 LOY. L.A. L. REV. 259, 288 n.154 (2007) (reporting that although Professor Steve Shiffrin believes the Court would strike down a tailored or a general moratorium, Shiffrin believes both should be upheld).

moratorium is needed in “exceptional” cases.¹² In the end, Congress did not adopt a moratorium, influenced by constitutional questions.¹³

A temporary moratorium for DTC advertisements for newly approved drugs presents a stronger case for being considered constitutional than the permanent ban at issue in *Western States*. The advertised drugs reach a wide audience and may be for chronic use, factors that increase the potential for harm. This paper suggests criteria for when a moratorium is needed based on specific risk factors, such as drugs for which risk signals were seen in preapproval testing, drugs for patients with special risks, and drugs in a new therapeutic class. The moratorium also seems appropriate when additional testing has been specifically required by the Agency, including when scientific experts have a substantial concern that the “available data indicates a potential for a serious risk” to a wide number of patients.¹⁴ The moratorium would be for a limited time to enable doctors and the Agency to make a better assessment of the postapproval risks, based on the improved postmarket surveillance system Congress has required. A disclosure in the commercial that there may be unknown safety risks would be difficult for viewers to assess, and it is not a substitute for the concern that Congress legitimately can have to prevent harm to the general public. Indeed, as the D.C. Circuit Court of Appeals recently found en banc, “[T]he democratic branches are better suited to decide the proper balance between the uncertain risks and benefits of medical technology, and are entitled to deference in doing so.”¹⁵ Moreover, when the Agency believes that a moratorium is needed to protect the public health, the government should seek to have the matter resolved directly by the Court. The matter is too important to leave to the implications of cases that did not squarely deal with safety risks to the general public.

The paper also provides an overview of the intense dispute about the legal and constitutional protections for manufacturers that initiate a wide

12. *See id. passim; see also infra* Part IV.C.

13. *See* 153 CONG. REC. S5764 (daily ed. May 9, 2007) (statement of Sen. Kennedy) (explaining that Senators had concerns about the constitutionality of a moratorium even when limited to extraordinary circumstances).

14. *See* 21 U.S.C. § 355(o)(3) (Supp. I 2006) (authorizing a requirement for additional studies, including a clinical trial when needed, and the establishment of dispute resolution procedures); *see also infra* Part IV.C.

15. *See* *Abigail Alliance for Better Access to Developmental Drugs v. Eschenbach*, 495 F.3d 695, 713 (D.C. Cir. 2007) (en banc). The court in *Eschenbach* found that terminally ill patients do not have a fundamental right under the Federal Constitution to assume the risk and obtain access to unapproved drugs that have not been proven to be safe, and that under the rational basis test, the elected branches deserve deference. *Id.* at 705–06, 713.

distribution of reprints about unapproved off-label uses of a drug. At one point, a federal district court found the distributions to be constitutionally protected when a manufacturer makes a disclosure that the use had not been approved by FDA.¹⁶ The court also found it would be “constitutional blackmail” for Congress to condition an exemption from the drug approval requirements on the manufacturer’s submission of an application to do additional studies that are needed if the manufacturer distributes reprints on off-label uses.¹⁷ Although the district court decision was vacated on the basis that the FDA Guidance Document and the statutory exemption were only an advisory safe harbor,¹⁸ the decision remains influential.

At the end of the Bush administration, the Agency issued a Reprint Guidance stating that the Agency did not intend to consider the nonpromotional distribution of reprints by a company with disclosures about the lack of FDA approval as establishing “intent” that the product be used for an unapproved use.¹⁹ Although the Agency position is ambiguous on whether it rests on statutory or constitutional grounds, or is an enforcement policy, if the Obama administration had revoked it, the stage would have been set for a constitutional challenge. That litigation could also have tested the difference between commercial speech and expressive speech that receives the highest First Amendment protections.

In a recent case, *Allergan v. FDA*,²⁰ the Obama administration stated that the Reprint Guidance “reflects FDA’s understanding” that the

16. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 74 (D.D.C. 1998).

17. Wash. Legal Found. v. Henney, 56 F. Supp. 2d 81, 87 (D.D.C. 1999), *vacated*, 202 F.3d 331 (D.C. Cir. 2000). The supplemental new drug application provisions were in 21 U.S.C. § 360aaa-3 (Supp. III 1994).

18. Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

19. Guidance for the Industry on 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, Notice of Availability, 74 Fed. Reg. 1696 (Jan. 13, 2009), *available at* www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm [hereinafter Reprint Guidance].

20. Complaint at 28–33, *Allergan v. FDA*, No. 1:09-cv-01879-JDB (D.D.C. Jan. 11, 2010) [hereinafter *Allergan Complaint*]. The case concerns the off-label use of Botox to treat spastic conditions, including those in children. Recently, Allergan settled a fraud and abuse case brought by the federal government concerning the marketing of off-label uses of Botox, and agreed to pay a \$600 million penalty and “drop its First Amendment lawsuit against . . . F.D.A.” Natasha Singer, *Maker of Botox Settles Inquiry on Off-Label Use*, N.Y. TIMES, Sept. 2, 2010, at A1.

distribution of reprints in accordance with the Guidance “is not unlawful.”²¹ According to the Agency the “nonpromotional” distribution of reprints by manufacturers does not show an “intended use” related to an unapproved purpose.²² The Reprint Guidance, though, has an inappropriately narrow position on what is “promotional,” and therefore needs to be revised.²³ In *Allergan*, the maker of Botox raised a broad claim that any FDA ban on advertisements or claims for an unapproved off-label use—even those not based on reprints—is unconstitutional when the claim is truthful and not misleading.²⁴ Moreover, FDA cannot constitutionally restrict the manufacturer’s truthful claims about off-label uses that are “widely accepted” and are reimbursed as “medically-accepted” in government programs.²⁵ The company also raised a narrower issue that the FDA should not be able to preclude a company from providing information to doctors about ways to reduce risks from an off-label use.²⁶ FDA, though, recognizes that companies can provide warning information about off-label risks in a nonpromotional way.²⁷ Because this case can be resolved on narrower grounds based on the appropriateness of adding risk information, the Court should not reach the broader constitutional issues. The Agency should also reconsider the Bush Reprint Guidance and its narrow test for what is promotional, even though that may give rise to constitutional challenges.

The scope of the issues raised in *Allergan* makes it appropriate to reexamine the broader question of when a manufacturer should be able to make claims or distribute reprints about an off-label use. This Article explores in Part V.D the kind of restrictions that should be accepted under the “safety-focused” proportionality test, suggested by the dissent in *Western States*,²⁸ when a company seeks to make wide distributions of

21. Defendant’s Reply in Support of Motion To Dismiss or for Summary Judgment and Response to Cross-Motion for Summary Judgment at 21–24, *Allergan v. FDA*, No. 1:09-cv-01879-JDB (D.D.C. Oct. 1, 2009) [hereinafter *Allergan* Government Reply].

22. *Id.* at 9–10.

23. *See infra* Part V.C.

24. *Allergan* Complaint, *supra* note 20, at 29 (claiming the First Amendment protects truthful nonmisleading speech about an off-label use even when made in a commercial advertisement).

25. *Id.* at 34–35.

26. *Id.* at 21.

27. *Id.* at 7, 20. FDA regulations also allow a drug company to add warnings in advance of FDA approval by filing a “change being effected” supplemental NDA with the Agency. *See* 21 C.F.R. § 314.70(c)(1) (2008).

28. *See* *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 378–87 (2002) (Breyer, J., dissenting).

reprints about off-label uses.²⁹ This approach builds on that accepted by Congress in the past as an alternative, although that approach led to complex and inconclusive litigation.³⁰ Under this alternative, the use of better disclosures, and Agency review of the disclosures, would be the first step. When manufacturers distribute reprints about studies on off-label uses funded by them, they should disclose factors that affect the assessment of the reliability of the reprinted article. This includes disclosures of funding of any “ghostwriters” who substantially contributed to the article but who are not listed as authors.³¹ The manufacturer should also be obliged to submit further data to the Agency to support the use when the disclosures indicate that the need for more study to evaluate a potential safety risk.

In theory, as discussed in Part V, an off-label use, based on studies and reprints from a medical journal, accompanied by disclosures, might with time even become generally recognized as safe and effective (GRAS/E) and not even need formal prior Agency approval.³² On the other hand, an off-label use described in reprints could raise potential safety risks beyond those considered when the drug was initially approved. Given this reality, to have general recognition, the postapproval experience and risks from off-label uses promoted by a manufacturer need to be monitored in a way that warrants an Agency role. The discussion in Part V closes by suggesting that Congress provide research incentives to encourage manufacturers to obtain approval of a supplemental new drug application (NDA) for an off-label use based on adequate research and postapproval risk surveillance. Congress should not be constitutionally limited to being able to require disclosures about potentially misleading claims and the possibility for added unknown risks. Exploring new approaches to deal with off-label promotion reflects the important role Congress and the Agency have to adapt the law to

29. The safety risk could exist because of the harm directly caused or could be an indirect risk because of weak support for a claimed health benefit.

30. See 21 U.S.C. § 360aaa-3 (Supp. III 1994) (expired pursuant to Pub. L. No. 105-115, 111 Stat. 2364 (1997), and 63 Fed. Reg. 64,556 (Nov. 20, 1998)); *supra* notes 16–18; *infra* Part V.A.

31. See Duff Wilson, *Medical Schools Quizzed on Ghostwriting*, N.Y. TIMES, Nov. 18, 2009, at B2 (criticizing as plagiarism articles written by those not named as authors); see also *infra* Parts III.A, V.D.

32. See *infra* Part V.A.1.

deal with new problems in a way that promotes the availability of safe and effective new uses for drugs.³³

The history of Vioxx, as discussed in this paper, illuminates not only the problem of postmarket risks but also the interplay between reprints and Agency review.³⁴ Merck, the manufacturer of Vioxx, actually sought FDA approval for an off-label use that had been favorably reviewed in an article in the *New England Journal of Medicine*.³⁵ The Agency found that the drug had a potential for causing cardiovascular risks, a potential that the *Journal* writers had discounted at the time.³⁶ The Agency required a precaution on the drug's label and further monitoring, and that monitoring demonstrated that the drug had an increased incidence of adverse cardiovascular effects.³⁷ The lesson drug companies might draw from this history, though, is that they should not seek Agency approval for an off-label use. Instead, they may fund research on the off-label use, encourage publication in a medical journal, and then rely on the First Amendment to justify distributing reprints to doctors with disclosures about the lack of FDA approval. That unfortunate result would be a loss for the public.

Drug manufacturers may have a special concern about a moratorium or restrictions on the distribution of reprints because they seek to reach the full market potential for the drug as soon as possible in order to recoup the large cost of drug development while the drug is still under patent. Although the business need should not trump safety or establish the scope of the First Amendment, the economic concern with the "ticking patent clock" needs to be recognized. If a policy solution is needed, though, it is one for Congress to consider. The legislature can investigate the seriousness of the concern and has means to address it in ways that are beyond the judicial sphere. For example, Congress might extend the brand drug's exclusivity for a limited period to reflect a

33. For an expansive view of the Agency's role in interpreting the law to promote the statutory purpose, see *United States v. Article of Drug, Bacto-Unidisk*, 394 U.S. 784, 798–800 (1969); *United States v. N.S. Food Prod. Corp.*, 568 F.2d 240, 246–48 (2d Cir. 1977); Peter Barton Hutt, *Philosophy of Regulation Under the Federal Food, Drug and Cosmetic Act*, 28 FOOD DRUG COSM. L.J. 177 (1973).

34. See Margaret Gilhooley, *Vioxx's History and the Need for Better Procedures and Better Testing*, 37 SETON HALL L. REV. 941, 947–51 (2007); see also *infra* Part III.B.

35. Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520, 1525–27 (2000).

36. David Armstrong, *The New England Journal Missed Vioxx Warnings Signs*, WALL ST. J., May 15, 2006, at A1 (describing different assessment and later retraction by the *Journal*).

37. Gilhooley, *supra* note 34, at 948–51.

moratorium on advertising.³⁸ Congress might also consider whether stronger research incentives are needed to encourage manufacturers to seek approval for new uses of marketed drugs, instead of distributing reprints about off-label uses.³⁹

This is an important time to reexamine the constitutional appropriateness of speech restrictions involving health and safety regulation. Academics are beginning to reassess and debate whether the constitutional protections for drugs go too far or are not extensive enough.⁴⁰ Drug regulation may also receive more public attention in the wake of the congressional efforts to reform health-care financing. Although major legislative changes typically occur after a tragedy or crisis, an understanding of the limits on Congress's power remains important. The position of this paper is that the safety concerns that underlie drug regulation are significant public interests that deserve more weight than the economic and competitive factors involved in most commercial speech litigation. Instead of a single general theory for commercial speech, there is a need

38. One approach might be to allow an extension of market exclusivity for a month or two in order to take into account the effect a moratorium has on the ability to recoup drug costs during the remaining patent term. *See infra* Part IV.D.

39. *See infra* Part V.G.

40. For concern about the scope of commercial speech, see Paul D. Carrington, *Our Imperial First Amendment*, 34 U. RICH. L. REV. 1167, 1188–92 (2001), identifying difficulties of extending commercial speech protections to DTC advertising; Margaret Gilhooley, *Constitutionalizing Food and Drug Law*, 74 TUL. L. REV. 815 *passim* (2000), criticizing constitutional limits on Congress's powers to restrict speech to protect against health risks; Earl M. Maltz, *The Strange Career of Commercial Speech*, 6 CHAP. L. REV. 161, 171 (2003), tracking the shift of support for the doctrine from liberals to conservatives and criticizing both for activism; Tamara R. Piety, *Against Freedom of Commercial Expression*, 29 CARDOZO L. REV. 2583, 2585–87 (2008), criticizing any expansion of commercial speech protections. For a discussion that restrictions on nondeceptive commercial speech should be “an extreme last resort,” see Symposium, *supra* note 10, at 347–48 (2007) (quoting remarks of Kathleen Sullivan, a self-described “strong supporter” of commercial speech). For support of a broader scope of constitutional protections for experimental drugs, see Richard A. Epstein, *Cancer Patients Deserve Faster Access to Life-Saving Drugs*, WALL ST. J., May 2–3, 2009 at A11. For a range of perspectives, see *Symposium on Commercial Speech and the Public Interest*, HEALTH MATRIX (forthcoming 2010), and *Symposium on Marketing Health: The Growing Role of Commercial Speech Doctrine in Health Regulation*, 37 AM. J. L. & MED. (forthcoming 2011). *See also* ASS'N OF AM. LAW SCHS., 2010 ANNUAL MEETING: CONSTITUTIONAL HEALTH LAW: PHARMACEUTICAL REGULATION AND COMMERCIAL SPEECH 8 (2010), available at <http://www.aals.org/am2010/brochure1.pdf>.

to “think small” about particular types of issues.⁴¹ From that perspective, regulation that affects public safety deserves special attention and weight.

To develop the analysis, Part II will provide an overview of the key elements of the statutory framework for premarket approvals and prescription statuses of drugs. That discussion will summarize the evolution of FDA’s policy for allowing DTC advertisements, a development influenced by the recognition of commercial speech protections.

Part III will review the reasons why postapproval risks are found for drugs notwithstanding the preapproval testing for them and review the Vioxx history. The recommendations of the IOM committee and the legislative changes to improve FDA’s ability to respond to postsafety risks will be summarized.

Part IV will explore the issues on whether a moratorium on television advertisements for newly approved prescription drugs would be constitutional. Although Congress considered a moratorium, it did not enact one. The discussion considers the differences between a moratorium and the pharmacy compounding at issue in *Western States*, and identifies the circumstances when a moratorium is most needed.

Part V considers the manufacturer’s distribution of medical reprints about off-label uses in light of the Agency’s policy on what is relevant to demonstrate an intended use for an unapproved purpose. The discussion covers the need for additional disclosures to ensure that the distribution is not misleading. The discussion also covers the extent to which the Agency should be able to require additional testing if the available information indicates that the new off-label use poses significant risks or needs postmarket surveillance. The role for research incentives will be noted.

The conclusion in Part VI reviews how a proportionality test provides a justification for delaying some television advertisements pending postmarket surveillance. Moreover, when the manufacturer widely distributes reprints about off-label uses, disclosures seem needed about factors that can affect the assessment of the reliability of the studies. The Agency should be able to require more studies, postmarket surveillance, and disclosures when needed to assess the risks, including factors that indicate that the drug does not have the safety benefit it claims to have. This paper provides an illustration of how a safety-focused proportionality test can work in practice and the challenges involved.

41. Steven Shiffrin, *The First Amendment and Economic Regulation: Away from a General Theory of the First Amendment*, 78 NW. U. L. REV. 1212, 1215 (1984).

II. LEGAL AND REGULATORY FRAMEWORK FOR DRUG APPROVALS, PRESCRIPTION STATUS, AND DTC ADVERTISEMENTS

This Part will provide an overview of the provisions that govern the testing needed for FDA approval of a new drug, the criteria governing the prescription status of a drug, and FDA guidance for advertising prescription drugs to consumers on television.

A. *History of Standards for Approval*

1. *Early Efforts To Prohibit Deception and the Challenges*

When the Federal Food and Drug Act was first enacted in 1906, it prohibited misleading labeling, but the prohibition was interpreted by Justice Holmes to apply only to misstatements of ingredients because of constitutional doubts about Congress's ability to regulate "where opinions are far apart."⁴² In 1916, the Court upheld a prohibition against "false and fraudulent" claims,⁴³ and in 1937, Congress once again barred misleading claims, a prohibition still in effect.⁴⁴ Material omissions are considered in determining deception. This time the prohibition was found to be constitutional when challenged.⁴⁵

2. *Preapproval Safety Requirement*

The law was strengthened in 1938 in response to a tragedy. Nearly ninety people died when a drug company used antifreeze as the inactive ingredient in a new liquid form of a sulfa drug without any testing or investigation of the risks.⁴⁶ Premarket testing for safety was required for drugs not generally recognized as safe, as well as a submission of a NDA to the Agency. The Agency's powers were weak, though, because the application was automatically approved after a waiting period if the Agency did not act.

42. *United States v. Johnson*, 221 U.S. 488, 498 (1911).

43. *Seven Cases of Eckman's Alt. v. United States*, 239 U.S. 510, 517 (1916).

44. 21 U.S.C. § 352(a) (2006); *see also id.* § 321(n) (2006) (making material omissions relevant in determining deception).

45. *Research Laboratories, Inc. v. United States*, 167 F.2d 410, 422–23 (9th Cir. 1948).

46. David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 LAW & CONTEMP. PROBS. 2, 20 (1939).

3. Modern Premarket Testing and Approval Requirements

In 1962, the sleeping pill thalidomide, which was pending review at FDA, was found to cause birth defects in Europe.⁴⁷ Congress responded by strengthening the statute in several ways, the first being that the Agency must affirmatively approve the drug before it can be sold. The law also went beyond requiring that the drug be safe by requiring that it be effective. Modern drugs have powerful ingredients that can cause harm, and the determination of safety has to be made on a risk-benefit basis. The law also required that the efficacy showing be based on “adequate and well-controlled investigations” contained in a NDA that show that the drug is effective as well as safe for its intended use.⁴⁸ The tests to obtain drug approval are lengthy and costly.⁴⁹ Nonetheless, the pharmaceutical industry is profitable, and in 2000, it was reported to be the most profitable industry in the country.⁵⁰

4. Concern with Faster Determinations

Congress and the Agency have sped up the process by providing for expedited approval of “fast-track” drugs, such as AIDS and cancer drugs, that treat unmet medical needs.⁵¹ The law has also provided that drug companies filing an NDA are to pay user fees to permit the Agency to hire more medical reviewers to enable more timely action on the application.⁵² The Agency has established goals for the time it should take to act on the NDA.⁵³ The user fees need to be renewed every five years, which leads to an opportunity for Congress to review the Agency’s approach to regulation. As a result, a number of changes and compromises have been added to the drug provisions to deal with contentious issues,

47. Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 191 n.45 (1971).

48. 21 U.S.C. § 355(d)–(e) (2006 & Supp. I 2006). For a history of the approval requirements, see Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753 (1996). For a description of the approval process, see James N. Czaban & Geoffrey M. Levitt, *Drugs: INDs and Full NDAs*, in FOOD AND DRUG LAW AND REGULATION 317, 318–19 (David G. Adams et al. eds., 2008).

49. See Tufts Ctr. for the Study of Drug Dev., *How New Drugs Move Through the Development and Approval Process* (Nov. 1, 2001), http://csdd.tufts.edu/files/uploads/how_new_drugs_move.pdf (discussing an \$800 million cost estimate over ten to fifteen years).

50. M. Angell, Editorial, *The Pharmaceutical Industry—To Whom Is It Accountable?*, 342 NEW ENG. J. MED. 1902, 1903 (2000).

51. 21 U.S.C. § 356 (2006); Margaret Gilhooley, *Heal the Damage: Prescription Drug Consumer Advertisements and Relative Choices*, 38 J. HEALTH L. 1, 8–13 (2005) (reviewing the scope of testing standards).

52. See PETER BARTON HUTT ET AL., FOOD AND DRUG LAW 678–84 (3d ed. 2007).

53. *Id.* at 679–81.

including the provisions on compounded drugs that were at issue in *Western States*.⁵⁴

B. Prescription Status

Since 1951, the law has expressly provided for limiting drugs to prescription status when the drug is not safe for use except under medical supervision because of its toxicity or “collateral measures.”⁵⁵ Collateral measures arise when a drug masks symptoms of a more serious condition and delays treatment.⁵⁶ Nonprescription drugs are the familiar ones, found on the shelves in drug stores and supermarkets, and sold over the counter (OTC). The underlying philosophy of prescription status is that adequate directions for lay use cannot be written.⁵⁷ That philosophy has some tension with the increased role that DTC advertising creates for patients.

C. DTC Advertisements and Role of Guidance Documents

The statute provides for advertising drugs to physicians, not consumers, and the statute calls for a “true statement” of information in a “brief summary” of the “side effects, contraindications, and effectiveness” of the drug.⁵⁸ The Agency regulations implementing this requirement called for disclosures that track the approved small-print labeling for the drug.⁵⁹ The need to cover all that information made any television advertising to doctors or consumers impractical.

“[F]aced with threats of legal challenge”⁶⁰ in 1995, FDA issued guidance documents providing alternatives that made DTC advertisements feasible. Although the nature of the legal challenge is not specified, it clearly would have been a commercial speech challenge. The revised guidance provided for identifying the “most important risk information” in

54. See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 364 (2002).

55. 21 U.S.C. § 353(b) (2006).

56. See *United States v. Article of Drug Labeled Decholin*, 264 F. Supp. 473, 483–84 (E.D. Mich. 1967).

57. See Peter Temin, *The Origin of Compulsory Drug Prescriptions*, 22 J.L. & ECON. 91, 97 (1979).

58. 21 U.S.C. § 352(n) (2006).

59. See HUTT ET AL., *supra* note 52, at 555–57.

60. *Id.* at 557.

the television advertisement and providing the full text of the drug labeling through a print advertisement in a consumer magazine or other means.⁶¹

The DTC advertisements can raise other problems. The advertisements may give the viewer an impression that the drug has a greater benefit than it has. Disclosures may be needed in the advertisement that the doctor may want to consider other drugs whose risks and benefits are better known.⁶² A “fact box” may be needed on the limited benefit that the advertised drug may provide.⁶³ The Agency is also seeking to limit commercials that use distracting images when warnings are given.⁶⁴ Although some may dispute whether these matters need regulation, they do not directly raise commercial speech issues when they involve deception, and thus the need for these changes is not the focus of this paper.⁶⁵

III. POSTAPPROVAL RISKS: LESSONS FROM VIOXX, THE IOM REPORT, AND LEGISLATIVE CHANGES ON SURVEILLANCE AND THE AGENCY’S AUTHORITY

This Part provides an overview of why drugs may be found to have additional risks after they are approved by FDA and the efforts to develop an appropriate response. The postmarket risks found for Vioxx, a widely used arthritis drug, are noted because the drug illustrates the problem with postmarket risks. The withdrawal of the drug from the market by the manufacturer led to public and legislative concern.⁶⁶ FDA asked the IOM to study drug safety and make recommendations.⁶⁷

61. *Id.* at 557–58; Gilhooley, *supra* note 51, at 17–20.

62. COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 171.

63. Lisa M. Schwartz et al., *Using a Drug Facts Box To Communicate Drug Benefits and Harms: Two Randomized Trials*, 150 ANNALS INTERNAL MED. 516 (2009); see Marvin M. Lipman, *Bias in Direct-to-Consumer Advertising and Its Effect on Drug Safety*, 35 HOFSTRA L. REV. 761 (2006) (providing a critical evaluation by the chief medical adviser for Consumers Union, the publisher of *Consumers Report*); Natasha Singer, *Prescriptions; Overhauling Drug Labels*, N.Y. TIMES, Nov. 7, 2009, A13 (reporting a health reform proposal to include a chart for drugs, like the nutritional labeling on foods).

64. Direct-to-Consumer Prescription Drug Advertisements; Presentation of the Major Statement in Television and Radio Advertisements in a Clear, Conspicuous, and Neutral Manner, 75 Fed. Reg. 15,376 (proposed Mar. 29, 2010) (to be codified at 21 C.F.R. pt. 202); FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PRESENTING RISK INFORMATION IN PRESCRIPTION DRUG AND MEDICAL DEVICE PROMOTION 5, 19–20 (2009).

65. FDA’s authority over health claims on foods and dietary supplements has also been restricted on commercial speech grounds, but the matter is not discussed here because the products are not drugs. See *Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999).

66. See *FDA, Merck, and Vioxx: Putting Patient Safety First?: Hearing Before the S. Comm. on Fin.*, 108th Cong. 49–57 (2004) (statement of Dr. Sandra Kweder, Acting Director, Office of New Drugs, Center for Drug Evaluation and Research) [hereinafter *Fin. Comm. Report*]; Gilhooley, *supra* note 34, at 941.

67. COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at ix.

Congress changed the law to provide for more postmarket surveillance of risks and expand the Agency's authority to require new warnings and additional testing. Congress considered but did not enact a moratorium on DTC advertisements, as discussed in the next Part.

A. Limits of Testing

FDA has long recognized the limits of the preapproval testing for drugs. In 1964, Commissioner George Larrick stated that the initial period of drug marketing represents "a final step in the testing of the product" and that there is "no way to duplicate fully in clinical trials the great variety" of conditions under which an approved drug will be used.⁶⁸

In the IOM Report, a committee of the IOM found that the limits on the ability to detect the full risks are "inherent" in the system and "cannot be changed without adding considerably to the time and expense of drug approvals, which would delay patient access to potentially beneficial drugs."⁶⁹ The studies are aimed primarily at establishing efficacy rather than safety.⁷⁰ The IOM Report also found that the preapproval studies do not provide information on long-term exposure, and they do not represent the "full array of the patients" who will use the drug including those with various illnesses.⁷¹ To deal with these drawbacks, the committee recommended improvements be made in the postmarket surveillance of the risks and the Agency's ability to act when new risks are found.⁷²

B. Vioxx as an Illustration of the Testing System

Vioxx has become the poster child for understanding the modern system of testing and its limits. An overview of its history is instructive on many issues, including medical articles about off-label uses.

68. *Drug Safety Part One: Hearings Before the Subcomm. of the H. Comm. on Gov't Operations*, 88th Cong. 152 (1964) (statement of George Larrick, FDA Comm'r), as reprinted in HUTT ET AL., *supra* note 52, at 686.

69. COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 38.

70. *Id.*

71. *Id.*

72. *Id.* 110–15, 169–70.

1. Initial Approval and Scope of Testing

Vioxx, which was made by Merck, was initially approved by FDA as a painkiller for acute and arthritis pain.⁷³ The studies needed to show that effectiveness in eliminating pain did not have to be lengthy studies, and one expert later testified about the limited scope of the testing done at the time of approval for a drug for chronic use.⁷⁴ An FDA reviewer did a meta-analysis of the various studies and found that the cardiovascular side effects were the most frequently reported serious adverse effects.⁷⁵ This observation was reported in the publicly available medical reviewer's summary but was not included in the labeling.

2. Bleeding Prevention Benefit Study and the New England Journal of Medicine (NEJM) Article

a. VIGOR Study

When Vioxx was approved for pain, there were some preliminary indications and hopes that, as a COX-2 inhibitor, it might reduce the serious problems of stomach bleeding that can occur with painkillers for chronic use. Merck sponsored the VIGOR study, a controlled outcome study, to show that it would have this benefit, in comparison to naprosyn, the existing alternative for arthritis pain. The benefit was shown, but Vioxx had a higher incidence of cardiovascular effects at a high dose.⁷⁶ That dose was above the level at which it was intended to be used but had been included in the test as a way to identify better its effectiveness.⁷⁷

b. NEJM Publication of the VIGOR Study

The NEJM published the results of the VIGOR study, whose chief researcher worked for Merck, with a favorable review.⁷⁸ The article attributed the higher incidence of cardiovascular effects to the “protective” effect of naprosyn. After the article was published, the use of Vioxx

73. U.S. Food & Drug Admin., *Sequence of Events with Vioxx, Since Opening of IND*, http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_04_E-FDA-TAB-C.htm (last visited June 12, 2010); Gilhooley, *supra* note 34, at 944–54.

74. *Ensuring Drug Safety: Where Do We Go from Here?: Hearing Before the S. Comm. on Health, Educ., Labor, & Pensions*, 109th Cong. 42, 98 (2005) (statement of Dr. Bruce Psaty, University of Washington, on the limited testing for a drug for chronic use).

75. See Gilhooley, *supra* note 34, at 946.

76. Bombardier et al., *supra* note 35, at 1520.

77. Gilhooley, *supra* note 34, at 947.

78. See Bombardier et al., *supra* note 35, at 1520, 1527.

expanded. Merck had also purchased most of the 900,000 reprints made of the article.⁷⁹

3. *FDA Action on Supplemental NDA*

Merck actually sought FDA's approval for the bleeding benefit shown by the VIGOR study by filing a supplemental NDA. The Agency agreed that the study supported the new efficacy claim but did not accept that naprosyn had a protective effect that accounted for the increased incidence of cardiovascular effects for Vioxx shown in the study.⁸⁰ After a long period of intense negotiation, the Agency approved the claim for the new benefit. However, it required a precaution in the label that cardiovascular effects were seen at a higher dose than that intended for use, that the significance was "unknown," and that no further study was being done.⁸¹

4. *Finding of Cardiovascular Effects and Withdrawal of Vioxx*

At FDA's request, Merck undertook to monitor the cardiovascular risks from Vioxx in an ongoing Merck study that aimed to show that the drug had a benefit in preventing colon cancer. During the study, the evaluators found that those receiving the drug had a statistically significant increased incidence of cardiovascular effects compared to the control group.⁸² Merck stopped the study and withdrew Vioxx from the market voluntarily because the life-threatening cardiovascular risks to the intended users outweighed the benefit that might be expected.⁸³

79. Armstrong, *supra* note 36, at A1 (reporting that the medical journal sold more than 900,000 reprints for at least \$697,000 and that Merck bought most of the reprints).

80. Gilhooley, *supra* note 34, at 947–48.

81. PHYSICIANS' DESK REFERENCE 2110 (58th ed. 2004); Gilhooley, *supra* note 34, at 948–49.

82. Memorandum from John K. Jenkins, M.D. & Paul J. Seligman, M.D., M.P.H. through Steven Galson, M.D., M.P.H. at 3 (Apr. 6, 2005), <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106201.pdf> [hereinafter Decision Memorandum]; Gilhooley, *supra* note 34, at 950.

83. Fin. Comm. Report, *supra* note 66, at 65 (statement of Raymond Gilmartin, Chairman, President and CEO of Merck); Gilhooley, *supra* note 34, at 950. A wide number of product liability suits were brought against Merck, but these are not the subject of this paper.

5. FDA Response on Class Effects

FDA found that the cardiovascular finding for Vioxx was best interpreted as a class effect that also applied to Celebrex, a COX-2 drug made by Pfizer.⁸⁴ In addition, the effect extended to nonsteroidal anti-inflammatory (NSAID) drugs like naprosyn, including its over-the-counter version, Aleve.⁸⁵ The Agency did not seek to withdraw all these drugs from the market and instead required a prominent boxed warning about the cardiovascular risk on all drugs in the class.

6. The Role of FDA Review and Journal Articles

The history of Vioxx illuminates how the Agency review process compares even to that for an elite journal. The NEJM later acknowledged that the finding of a protective effect for naprosyn was incorrect.⁸⁶ It also illustrated the different interpretations that can be made by experts in making scientific assessments about controlled studies and the limits those studies can have. That experience would seem to show the value of both types of review.

C. Congress's Legislative Response

The withdrawal of Vioxx and the cardiovascular warnings for NSAID drugs created widespread public concern. At FDA's request, an IOM committee made recommendations. Congress enacted changes in the law to improve postmarket surveillance and expand the Agency's authority in many of the ways discussed in the IOM Report. Congress's nonaction on a moratorium for DTC advertisements is discussed in the next Part.

1. Electronic Surveillance and Testing Requirements

Congress acted to improve the Agency's ability to find postmarket risks and authorized the Agency to establish a "Postmarket Risk Identification and Analysis System."⁸⁷ This active surveillance system's purpose is to datamine the electronic records of Medicare and the records of private insurers, when available.⁸⁸ The aim was to have the

84. Decision Memorandum, *supra* note 82, at 2.

85. *Id.* at 11.

86. Armstrong, *supra* note 36, at A1. See Gilhooley, *supra* note 34, at 948.

87. FDA Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, 945 (2007) (codified as amended at 21 U.S.C. § 355(k)(3)(C) (Supp. I 2010)).

88. COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 114; Margaret Gilhooley, *Addressing Potential Drug Risks: The Limits of Drug Testing*,

system cover the records of 100 million patients by 2012.⁸⁹ The drug manufacturers pay “user fees” to provide the financial resources to enable the government to establish the new surveillance system.⁹⁰

2. *Expanded Agency Authority*

a. *Requirements for New Testing and Warnings*

Congress gave the Agency specific authority to require postmarket studies, including clinical studies, for newly approved drugs if needed to assess risk signals and “to identify an unexpected serious risk when available data indicates the potential for a serious risk.”⁹¹ Similar studies can be required for drugs already on the market if there is “new safety information.”⁹² The Agency must establish dispute resolution procedures to permit appeals by those who disagree with the requirement.⁹³

As part of a risk evaluation and management strategy, the Agency can also require warnings about new safety risks.⁹⁴ The Agency did not have this specific authority earlier and had to negotiate changes that led to the criticism that the precaution given about the cardiovascular risks from Vioxx was “tepid.”⁹⁵ The Agency can also find that, as part of a strategy, there is a need for patient labeling or a “communication plan” with doctors.⁹⁶ No provision is made, though, for a DTC moratorium.

b. *New Enforcement Authority*

The Agency also cited the procedural hurdles it has faced in taking tough enforcement action. A formal administrative process is required

Risk Signals, Preemption, and the Drug Reform Legislation, 59 S.C. L. REV. 347, 363–64 (2008).

89. See 21 U.S.C. § 355(k)(3)(B)(i)(II) (Supp. I 2007).

90. Gilhooley, *supra* note 88, at 363.

91. 21 U.S.C. § 355(o)(3)(B) (Supp. I 2007). Electronic surveillance must not be sufficient to assess the risk.

92. 21 U.S.C. §§ 355-1(b)(3)(A), 355(o)(3)(C) (Supp. I 2007); Gilhooley, *supra* note 88, at 364–65.

93. 21 U.S.C. § 355(o)(3)(F) (Supp. I 2007).

94. 21 U.S.C. § 355(o)(4) (Supp. I 2007).

95. See Marcia Angell, *Your Dangerous Drugstore*, N.Y. REV. BOOKS, June 8, 2006, available at <http://www.nybooks.com/articles/archives/2006/jun/08/your-dangerous-drugstore/>.

96. 21 U.S.C. § 355-1(e) (Supp. I 2007).

to remove an approved drug from the market because of safety risks.⁹⁷ When the Agency believes the labeling is misleading because it fails to warn of a new risk, the Department of Justice or U.S. Attorney brings the lawsuit to make the legal challenge on this basis.⁹⁸ Congress has now authorized the Agency to bring an administrative proceeding to impose substantial civil money penalties if a manufacturer fails to comply with a requirement to do more testing or to add a warning.⁹⁹

The next Part deals with the nonenactment of a DTC moratorium and the constitutional issues that played a role in not enacting the moratorium.

IV. CONGRESS'S NONADOPTION OF A MORATORIUM ON DTC ADVERTISEMENTS: WOULD A MORATORIUM BE CONSTITUTIONAL?

When Congress strengthened the law to deal with the potential for postmarket safety risks dramatized by Vioxx, Congress did not include a moratorium on DTC advertising because of concerns about its constitutionality. The discussion in this Part examines *Western States* for its relevance on the constitutionality of a moratorium and other speech restrictions on drugs. The discussion will then examine the scope of a moratorium that is most proportional to the need.

A. IOM Recommendation and Debate: Moratorium for Specific Risks and During the Initial Period

Overall, the IOM's recommendations on improving postapproval risk assessment for drugs covered a number of measures that the Agency should be able to require, including additional drug safety testing and a moratorium on DTC advertising. These measures were to "match the specific safety concerns and benefits presented by the drug product."¹⁰⁰ In a separate recommendation, the IOM stated that FDA "should restrict" DTC advertising in the initial period after a drug is approved.¹⁰¹ According to the committee, that delay may be needed because the advertising has the ability "to dramatically increase the uptake of a newly approved drug [and in some cases,] expose larger numbers of

97. 21 U.S.C. § 355(d) (2006). A hearing can be held after a suspension for an imminent hazard but that requires a nondelegable determination by the Secretary.

98. See Gilhooley, *supra* note 34, at 957.

99. 21 U.S.C. § 333(f)(4) (Supp. I 2007); Gilhooley, *supra* note 88, at 365–66.

100. COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 169.

101. *Id.* at 171. The period was tied to the time when a special symbol would appear in the physician labeling to indicate that the drug was new.

people” to potential risks.¹⁰² The committee stated that it “would favor imposition of a formal moratorium,”¹⁰³ but recognized that it might be “inconsistent with First Amendment protections of commercial speech” and supported disclosures on the limits of the data if that were the case.¹⁰⁴ In the end the Senate did not include a moratorium in the law, with Senator Kennedy explaining that Senators had concerns about its constitutionality.¹⁰⁵

*B. Constitutionality of a Moratorium and Western States:
What Difference Does Safety Make?*

1. Commercial Speech Prongs

The framework for the general analysis of commercial speech cases is the one identified in *Central Hudson*: that the government must have a substantial government interest, the restriction in question directly advances that interest, and it must not “be more extensive than necessary.”¹⁰⁶

The commercial speech cases in the Supreme Court have largely involved permanent limits on price advertisements by competitors and advertising limits on professionals and other types of economic regulation that generally have not dealt with public safety.¹⁰⁷ The ability to relate the cases to the drug context can be difficult. Thus, in determining the need for a moratorium, a precedent exists in the Court’s upholding a limited thirty-day time bar on lawyers contacting the families of those killed in accidents.¹⁰⁸ The need for that delay relates to the common human experience of grief. The reason for a moratorium on drug advertisements relates to a scientific model that puts the burden for testing on the maker of a new claim. The Supreme Court has also dealt with commercial speech restrictions with a safety rationale in the case of state restrictions on the promotion of tobacco in an effort to protect youths. However, the restrictions created a spillover effect on the ability to advertise to adults

102. *Id.*

103. *Id.*

104. *Id.*

105. 153 CONG. REC. S5764 (daily ed. May 9, 2007) (statement of Senator Kennedy).

106. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 564 (1980). The first prong prohibits false, misleading, or unlawful speech, but this is rarely at issue. *See id.*

107. *See Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 365–68 (2002).

108. *Fla. Bar v. Went for It, Inc.*, 515 U.S. 618, 620 (1995).

that is not involved with a moratorium that is aimed at protecting the intended users.¹⁰⁹

2. *Western States and Its Scope*

The most pertinent case in examining how commercial speech applies to FDA health and safety regulation is *Western States*.¹¹⁰ Although the case dealt with an advertising ban for a limited category of compounded drugs made by pharmacies, the Court noted objections that will arise if a moratorium on DTC advertisements were required. The case illustrates the importance of identifying the government interest and the support to show that advertisements to patients pressure doctors to prescribe certain medications. The key prong, though, turns out to be the last one on whether a disclosure about a risk is an adequate alternative to protect the public from harm.

a. Nature of Compounding and Reason for Restriction

Pharmacies have long mixed ingredients or altered drugs to make a medication suited to the needs of an individual patient based on a doctor's prescription.¹¹¹ FDA believed compounding was appropriate and within the traditional practice of pharmacies when compounds were made for individuals who have special medical needs not met by available drugs, such as special dosage needs or allergies to a particular ingredient. However, FDA was concerned about the expansion of compounding to include variations of existing drugs and especially so when the variation is done on a widespread basis or with the use of commercial grade equipment. In line with FDA's policy, Congress exempted compounding from any need for new drug approval when done by a pharmacist in conjunction with a doctor's prescription for an identified patient, subject to conditions, such as that it not be done in "inordinate amounts" or be "essentially copies of commercially available drugs."¹¹² The key condition was that there be no advertisement to patients of the compounding for specific drugs, although advertisements about the availability of compounding services were acceptable.¹¹³

109. *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 528–29 (2001).

110. *Western States*, 535 U.S. at 357.

111. *Id.* at 360–61.

112. 21 U.S.C. § 353a(b)(1)(D) (2006).

113. *Id.* § 353a(c) (2006).

b. The Central Hudson Test and the Majority's Initial Analysis of the Test

The majority and the dissent differed on the basis for the government's action and the support for it. This led to a complicated level of analysis, which needs to be sorted out to understand the rigor of the test that may apply in future disputes.

i. Substantial Government Interest

The Court accepted that the government had identified a substantial interest in protecting the integrity of the new drug approval process while preserving the availability of compounded drugs for particularized medical needs.¹¹⁴

ii. Directly Advancing the Interest

The Court also assumed that an advertising ban would preclude large-scale manufacturing and thus "might" directly advance the line-drawing aim.¹¹⁵

iii. More Extensive than Necessary

The problem was that the government had failed to show the ban was "not more extensive than necessary."¹¹⁶ The aim could be met by nonspeech alternatives such as banning large-scale manufacturing equipment for compounding, a measure FDA had identified in an earlier policy statement. The Court also made the unusual suggestion that the government cap the profit in a specific period.¹¹⁷

c. The Dissent's Identification of Safety as the Government's Interest

i. Safety Interest

The dissent by Justice Breyer identified another substantial government interest for the advertising restriction: reducing the aggregate safety risk

114. *Western States*, 535 U.S. at 368–69.

115. *Id.* at 371.

116. *Id.*

117. *Id.* at 372.

from the unnecessary use of untested compounded drugs.¹¹⁸ A ban on the use of large-scale manufacturing equipment that the majority suggested as an alternative would not have served this additional safety interest because the harm could still occur if pharmacies used smaller-scale equipment.

ii. Advancing the Government's Interest: Effect of Advertisements on Pressure and Adequacy of Risk Explanation

Congress's restriction on advertisements for compounding would ensure that the decision about using an untested compound would be made by the prescribing physician based on the patient's need for it, without having the patient be influenced by an advertisement for a compound that might be only a convenience. To show the influence of advertisements, the dissent cited surveys by the Kaiser Health Foundation done with respect to DTC advertisements. The surveys showed that 71% of family doctors believe the DTC advertisements "pressure[] physicians into prescribing drugs they would not ordinarily prescribe."¹¹⁹ Another difficulty with the advertisements identified by the dissent was that they might "not fully explain the complicated risks at issue."¹²⁰

d. Response by Majority

i. Hypothesized Government Interest and Inadequate Showing

The majority rejected the dissent in ways that illuminate the rigor of the commercial speech standard for drug advertising. The government had not maintained that the advertising ban was needed to prevent the use of unnecessary drugs, and commercial speech protections were "significantly stricter" than the rational basis test by requiring the government to identify a substantial interest expressly.¹²¹ The dissent's contention that the advertisements lead doctors to prescribe unnecessary drugs rested on a "questionable assumption" based merely on one survey and one magazine article. For the majority, this was not sufficient to show that the restriction would "directly advance[]" the government's concern.¹²²

118. *Id.* at 380 (Breyer, J., dissenting).

119. *Id.* at 384. The survey was by the Kaiser Health Foundation, and the magazine was *Prevention Magazine*. *Id.* at 383–84.

120. *Id.* at 387.

121. *Id.* at 373–74 (majority opinion).

122. *Id.* at 374.

ii. Disclosures as Alternative

To the extent the dissent was suggesting that the advertisements would confuse consumers about the risks that might exist, instead of banning the advertisement, the “far less restrictive alternative” could be requiring a disclosure that the compounded drug had not undergone FDA testing and that its risks were “unknown.”¹²³ The First Amendment calls for a skepticism about restraints on truthful statements that “seek to keep people in the dark . . . for their own good.”¹²⁴

e. The Dissent on Congress’s Role and Commercial Speech

In his dissent, Breyer maintained that the commercial speech test needs:

[A] more lenient application . . . that reflects the need for distinctions among contexts, forms of regulation, and forms of speech Otherwise, an overly rigid “commercial speech” doctrine will transform what ought to be a legislative or regulatory decision about the best way to protect the health and safety of the American public into a constitutional decision prohibiting the legislature from enacting necessary protections.¹²⁵

Notably, then-Justice Rehnquist joined the dissenters in *Western States*. He was the sole dissenter when the Court extended First Amendment protection to commercial speech in a case striking down a state prohibition on drug price advertising.¹²⁶ Then-Justice Rehnquist called the Court’s approach “Lochnerian” and maintained that the free speech protections exist to protect “public decisionmaking as to political, social, and other public issues,” not commercial advertisements for shampoos or drugs.¹²⁷ Perhaps the safety concerns that arise with drug advertisements may have led him to agree on the need for a test that gives safety more significance.

C. Constitutionality of a DTC Moratorium After Western States

If Congress were to reconsider enacting a moratorium on DTC advertisements, the moratorium’s scope would be an important issue. The

123. *Id.* at 376.

124. *Id.* at 375 (citing 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996)).

125. *Id.* at 389 (Breyer, J., dissenting).

126. *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 781–90 (1976) (Rehnquist, J., dissenting).

127. *Id.* at 787.

Court is unlikely to overrule its precedents, but it may recognize important distinctions. The safety concerns that influenced the dissent may potentially get more recognition in cases in which the risks are even clearer.

When Congress was considering the legislative changes, the need for a moratorium was debated among medical experts¹²⁸ as well as legal experts.¹²⁹ Some believed that a tailored moratorium would be upheld when there was a reason to suspect risks from “specific, potentially high-risk drugs”¹³⁰ but that a categorical moratorium based on uncertainty would be found unconstitutional.¹³¹ Another legal scholar believed that the Court should uphold both a tailored moratorium and a categorical one but would not do so.¹³²

The discussion below outlines when a moratorium seems most needed and whether it would satisfy the prongs of the commercial speech test. The focus is on the constitutional test and not on whether the agency would have authority to require a moratorium under present law. The analysis also has relevance in understanding how a safety-based proportionality test may apply in connection with other speech restrictions including the distribution of reprints. Moreover, even apart from the constitutional issue, Congress and agencies should only regulate when there is a reasonable need to do so, and the test has some relevance in that determination.

1. Substantial Government Interest in a Temporary Moratorium

a. Criteria and Special Factors

A moratorium is most readily justified when it is directed at drugs that have identifiable, specific risk factors for added serious risks. Identifying special factors like these turn upon expert medical and scientific judgment. Still, the category would seem to appropriately include drugs

128. Miriam Shuchman, *Drug Risks and Free Speech—Can Congress Ban Consumer Drug Ads?*, 356 NEW ENG. J. MED. 2236 (2007).

129. See Symposium, *supra* note 10, at 335–57.

130. See Vladeck, *supra* note 11, at 276–82 (describing a legislative proposal by Senator Kennedy for a moratorium on a tailored basis for particular drugs).

131. See Mark I. Schwartz, *To Ban or Not To Ban—That Is the Question: The Constitutionality of a Moratorium on Consumer Drug Advertising*, 63 FOOD & DRUG L.J. 1 (2008) (analyzing reasons why the Court would be unlikely to find a blanket moratorium to be constitutional); Vladeck, *supra* note 11, at 288 (citing Professor Post).

132. See Vladeck, *supra* note 11, at 288 & n.154 (citing Professor Steve Shiffrin’s clarification of his remarks in Shuchman, *supra* note 128, that although he believes the Court would strike down a tailored or general moratorium, both should be upheld).

for which risk signals for serious harm were seen in the preapproval tests, as illustrated by the cardiovascular signals found for Vioxx. Another potential candidate would seem to be drugs for patients with serious acute medical conditions who are more susceptible to harm from unexpected additional risks.

A moratorium would also seem needed for drugs in a new therapeutic class that have a novel mechanism of action. The novelty itself suggests the potential for new risks that can warrant a delay in the DTC advertisements. The COX-2 inhibitors, like Vioxx and Celebrex, had a novel approach, which would seem to represent a new therapeutic class with potential risks.¹³³ The need for a moratorium for every new molecular entity is not clear. A moratorium may not be needed, for example, for a drug that is a minor variation or an isomer of an earlier drug, although the use of a higher dose could affect the assessment.¹³⁴ The evaluation of the need turns on a medical research judgment.

b. Scientific Uncertainty and Public Safety

A broader approach—having a moratorium during the initial period of use even in the absence of specific risk factors—should also be considered because of substantial scientific uncertainty about the potential for postapproval risks and its effect on public safety.¹³⁵ The law now allows FDA to require additional postapproval studies to “identify an unexpected serious risk when available data indicates the potential for a serious risk.”¹³⁶ The Agency has to provide for dispute procedures.¹³⁷ When the Agency has made such a finding, a moratorium may also be needed. A moratorium permits a better assessment of the additional information before advertising increases demand by a wide public. If the experience with postmarket testing shows that significant serious and unexpected risks are found, there is even a stronger basis for finding that a regular

133. See *supra* Part III.B.2 (describing Vioxx’s Bleeding Prevention Study).

134. Gilhooley, *supra* note 51, at 3, 26–27. Gilhooley describes reports that the head of Medicare regarded Nexium to be a “game” on those who pay for drugs. *Id.* at 3. Moreover, Nexium had a higher dose level and some added effect. *Id.* at 27–28. Finally, a scientist commented that Nexium was “identical” to the earlier drug, Prilosec, that he had developed. *Id.* at 26–27.

135. See *supra* Part IV.A; see also COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 171.

136. 21 U.S.C. § 355(o)(3)(B)(iii) (Supp. I 2006); see *supra* Part.III.C.

137. 21 U.S.C. § 355(o)(3)(F) (Supp. I 2006).

moratorium is warranted during the initial period of sale like that recommended by the IOM.¹³⁸

The duration of the moratorium is also important to determining its proportionality. The aim is to permit evaluation of the risk found after marketing, based on the improved means of postmarket surveillance and testing established by Congress. A two-year time frame for the moratorium seems appropriate as a starting point, with the Agency being able to shorten or lengthen it based on experience and the indicated need.¹³⁹ The electronic surveillance and other measures to track postmarket risk are still new, and how well they will work may have an important effect on the duration of the length of the time frame.

2. *Directly Advancing the Government Interest and Showing of Impact on Doctors*

The rigor of meeting the “directly advance” step has increased in recent cases. FDA has to show that the restriction “directly and materially advances” its interest, and must show that the harms it seeks to prevent “are real and that its restriction will in fact alleviate them to a material degree.”¹⁴⁰ Although that might be viewed as requiring a showing of empirical evidence, the Court has also recognized that in some settings this test can even be met “solely on history, consensus, and ‘simple common sense.’”¹⁴¹

In the case of DTC advertisements, the added difficulty in meeting this prong for prescription drugs is in showing that a consumer advertisement would pressure the doctor into acting differently. Justice Breyer, in his dissent in *Western States*, maintained that advertisements about compounding by pharmacies influence doctors, citing surveys from the Kaiser Health Foundation on DTC advertisements and the amount of money spent on the advertisements.¹⁴² Justice O’Connor found the assumption that doctors would be pressured by advertisements to be “questionable” and based on only one survey and magazine article, but ultimately did not rely on the adequacy of the showing to resolve the case.¹⁴³

138. See COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 171.

139. *Id.*

140. *Greater New Orleans Broad. Ass’n v. United States*, 527 U.S. 173, 188 (1999) (citing *Edenfield v. Fane*, 507 U.S. 761, 771 (1993)). See Vladeck, *supra* note 11, at 268–69 (summarizing ways that the test has become more rigorous).

141. *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 555 (2001) (citing *Fla. Bar v. Went for It, Inc.*, 515 U.S. 618, 628 (1995)).

142. See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 383–84 (2002) (Breyer, J., dissenting); see also Part IV.B.2.

143. *Western States*, 535 U.S. at 374–75 (majority opinion).

FDA also has stated in recent guidance that DTC advertisements can be misleading because they contain distracting images when warnings are given.¹⁴⁴ In support of its guidance, the Agency cited its 2004 survey of doctors about DTC advertisements that “almost half of physicians feel some pressure to prescribe as a result of DTC advertising, and patients and physicians report a belief that these ads overstate the drug product’s efficacy and do not present a fair balance of risk information.”¹⁴⁵ A randomized study also found that a patient who requests a specific drug is more likely to receive it than one who does not make such a request, even though they describe similar symptoms.¹⁴⁶ The amount spent on DTC advertising by itself is also an indicator of the influence it has. The spending reached \$4.1 billion in 2005, compared to \$12 million in 1997.¹⁴⁷

3. *Disclosures as an Adequate Alternative*

Still, the determinative issue is likely to be whether a moratorium is more extensive than necessary because a disclosure to consumers about the potential for additional risks may be an adequate alternative. An important problem with the disclosure approach, though, is that until more information is available about the postapproval risk, the doctor cannot make a fully confident decision on how widely the drug should be used. DTC advertisements can minimize the doctor’s role and might seem to put the burden on the doctor to justify why a drug should not be used in the face of uncertainty and emerging information. For newly approved drugs with risk factors, though, until more is known, the doctor should have the initiative to determine the patients for whom the drug is appropriate based on individual factors. In any case, it is reasonable for Congress to decide that approach is better.

144. FOOD & DRUG ADMIN., *supra* note 64, at 5.

145. *Id.* at 2 n.4 (citing KATHRYN J. AIKIN ET AL., U.S. DEP’T OF HEALTH & HUMAN SERVS., PATIENT AND PHYSICIAN ATTITUDES AND BEHAVIORS ASSOCIATED WITH DTC PROMOTION OF PRESCRIPTION DRUGS—SUMMARY OF FDA SURVEY RESEARCH RESULTS, 2–8 (2004), available at <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/DrugMarketingAdvertisingandCommunicationsResearch/UCM152860.pdf>. Regarding a preliminary survey on whether patients would seek the drug from other doctors, see Gilhooley, *supra* note 51, at 18 n.79.

146. Richard L. Kravitz et al., *Influence of Patients’ Requests for Direct-to-Consumer Advertised Antidepressants*, 293 J. AM. MED. ASS’N 1995, 1999 (2005) (reporting results of actors who went to a doctor’s office describing similar symptoms).

147. HUTT ET AL., *supra* note 52, at 558 n.1 (citing Rich Thomaselli, *Nothing but Blue Skies?*, ADVERTISING AGE, Oct. 2, 2006, at 3, 51).

Simply providing for a disclosure that there may be additional risks will tend to be a boilerplate statement that does not convey the complicated judgment the doctor has to make. If the commercial speech doctrine necessitates the disclosure alternative, the advertisement should reflect the one recommended by the IOM that the data on the risks and benefits from the advertised drug “are less extensive” than alternatives with longer use.¹⁴⁸ Moreover, the advertisement should expressly state that in some cases doctors may want to advise “caution” until more risk information is available.¹⁴⁹

4. *Wider Public Health Impact: Differences from Western States*

The larger picture is that television advertisements for prescription drugs have a greater potential to impact the public at large. The advertisements reach a larger audience. The drugs generally involve new molecules or have some new use. *Western States* dealt with a more limited potential for risk to the public health, from special compounds to meet individual needs, as well as a permanent ban on consumer advertisements. When the Agency believes a temporary moratorium is needed to protect the public health, the government should pursue efforts to require one. The public interest in a moratorium should be resolved on its merits in a direct test, rather by reading the implications of cases with a more limited focus.

D. *Ticking Patent Clocks and a Moratorium*

A moratorium aimed at protecting consumers will likely have an economic impact on drug companies. The companies believe they need to make enough revenues while the drug is under patent to finance the cost of additional research on beneficial products. Although the need to recoup the cost of drug development is important, it should not preclude measures needed to protect the public. Congress should examine directly whether some adjustment should be made. Congress has provided patent and nonpatent extensions to deal with circumstances found legislatively convincing, such as a limited extension in patent life to reflect the time

148. COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *supra* note 7, at 171.

149. *Id.* (recommending that the advertisement include “a caution” to speak to one’s doctor “about alternatives”).

needed to obtain FDA approval for a drug.¹⁵⁰ Generous intellectual property protections are available to encourage pediatric testing for drugs.¹⁵¹

A possible approach for Congress to consider, if a solution is needed, is to provide some type of nonpatent extension before generics can be sold for drugs subject to a moratorium. This extension, for example, might allow a one-month nonpatent extension for each year of the moratorium on DTC advertising. Although this extension would delay generics, the moratorium is part of a larger effort financed by the brand drugs to improve the safety of the drug. The brand drugs, for example, must pay user fees to finance the improved surveillance system to permit a better detection of postapproval risks, and they may have to do postapproval studies.¹⁵² The moratorium is to permit doctors to have a better understanding of the postapproval risks before the drugs are promoted to consumers. Any additional risks found would be reflected in the advertisements in the extended period. A small delay in generic availability can help balance the cost of providing this additional assurance of the safety of the brand drug and its generic version.

The extension should not, of course, be an exact match for the length of the moratorium. The drug company can sell the drug while the moratorium applies and can promote it to doctors. Moreover, it ensures that the drug is promoted in a way that reduces the potential for risks, which is an important concern.

V. REPRINTS ON OFF-LABEL USES AND COMMERCIAL SPEECH

This Part will start with a brief history of a complicated, important, and unresolved issue on the extent to which constitutional protections apply to manufacturer-distributed reprints of medical articles of studies funded by the company about an off-label use of an approved drug. The paper will discuss the Reprint Guidance Document issued by the Bush administration indicating that the Agency does not intend to consider nonmisleading distributions by a company of reprints about an off-label

150. 35 U.S.C. § 156(g)(6)(B) (2006); Rebecca S. Eisenberg, *Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development*, 72 FORDHAM L. REV. 477, 483 (2003).

151. See *Nat'l Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37, 38–40 (D.D.C. 1999); LARS NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY 879–80 (2d ed. 2007).

152. Gilhooley, *supra* note 88, at 363; see also FDA Amendments Act of 2007, Pub. L. No. 110-85, § 905(d), 121 Stat. 823, 949.

use of the drug to doctors as showing “intent” that the product be used for an unapproved use.¹⁵³ The paper will examine the questionable and ambiguous legal basis for the Reprint Guidance’s position on whether a distribution is evidence of intent for an unapproved use. This dispute also highlights the importance of the characterization of the manufacturer’s activity as promotional or part of a scientific exchange of ideas. If the Obama administration revised the Reprint Guidance, a constitutional challenge may follow, including whether the distribution is commercial speech or public speech that receives more protection. The *Allergan* case may also raise these issues.¹⁵⁴

This paper maintains that manufacturer-initiated general distributions of reprints are in many cases rightly regarded as a promotion of an unapproved use. In light of the unresolved issues and the dissent’s proportionality test in *Western States*,¹⁵⁵ this Part will consider whether manufacturer-initiated distribution of reprints on off-label uses are acceptable in some limited circumstances without Agency approval. This effort will consider whether an off-label use could have studies that are sufficiently reliable that the use could potentially become generally recognized as safe and effective (GRAS/E), and thus, by definition, not be new drug use.¹⁵⁶ An Agency policy based on that potential for GRAS/E recognition, though, would involve adequate disclosures by the manufacturer with the distribution about factors that affect the reliability of the study, some prior review of the disclosures by the Agency, and supplemental testing and postmarket surveillance when needed.

A. *History of Constitutional Dispute and WLF Litigation*

Sharp divisions exist on the extent to which commercial speech protects drug manufacturers who send doctors reprints from medical journals of articles about unapproved uses of the manufacturer’s drug. FDA has long accepted that doctors may use approved drugs “off-label” as part of the traditional practice of medicine based on their professional judgment and medical articles.¹⁵⁷ FDA also accepts that drug companies

153. Reprint Guidance, 74 Fed. Reg. 1694 (Jan. 13, 2009).

154. See *Allergan v. FDA*, No. 1:09-cv-01879-JDB (D.D.C. Jan. 11, 2010); *supra* note 20.

155. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 388–89 (Breyer, J., dissenting).

156. 21 U.S.C. § 321(g) (2006).

157. See *Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration: Notice of Proposed Rulemaking*, 37 Fed. Reg. 16,503 (Aug. 15 1972); Gilhooley, *supra* note 40, at 828–32.

may distribute reprints of journal articles about an off-label use in response to an unsolicited request from a doctor.¹⁵⁸

On the other hand, in the past, the Agency advised that manufacturer-initiated distributions about an off-label use would be impermissible when they were intended to promote the drug for an unapproved use.¹⁵⁹ The Agency position, though, was found to violate commercial speech protections in 1998 by a district court in a lawsuit brought by the Washington Legal Foundation.¹⁶⁰

In 1997, Congress enacted a “safe harbor” that exempted the manufacturers who distributed reprints on new uses from needing prior approval if the manufacturer submitted a supplemental NDA to the Agency to undertake any additional studies that were needed.¹⁶¹ When the statute was challenged, the district court regarded the provision calling for submission of a supplemental NDA as “constitutional blackmail.”¹⁶² The decision was vacated by the court of appeals without reaching the merits on the basis of the Agency’s position that the statute and Agency guidance were safe harbors and not binding determinations of the legal requirements for all distributions.¹⁶³ In the aftermath of the decision, it became “common” for drug companies to send out reprints on an off-label use with a disclosure about the lack of Agency approval, and “FDA did not attempt to stop them.”¹⁶⁴ This “[b]ehavior on the ground” has been seen as “the best indicator of perceptions of the state of the law.”¹⁶⁵

158. 61 Fed. Reg. 52,801 (Oct. 8, 1996). This dispute also encompasses continuing medical education (CME) programs organized by independent organizations funded by drug manufacturers. The CME issue is not dealt with here.

159. *Id.*

160. See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 74 (D.D.C. 1998), *amended sub nom. Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81, 87 (D.D.C. 1999), *vacated in part and appeal dismissed*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

161. 21 U.S.C. § 360aaa-3 (Supp. III 1994) (expired pursuant to Pub. L. No. 105-115, 111 Stat. 2364 (1997), and 63 Fed. Reg. 64,556 (Nov. 20, 1998)). Although this provision has expired by its terms, it can still be influential as a benchmark. For background, see Czaban & Levitt, *supra* note 48, at 405–08.

162. *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d at 87.

163. *Wash. Legal Found. v. Henney*, 202 F.3d at 331; Czaban & Levitt, *supra* note 48, at 405–08.

164. Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 1557, 1559 (2009).

165. *Id.*

B. *Bush Administration Reprint Guidance*

In the closing days of the Bush administration, the Agency issued a final Reprint Guidance document recognizing that the “public health can be served” when doctors receive journal articles on unapproved uses.¹⁶⁶ In the case of manufacturer-initiated distributions of a reprint about off-label uses, the Agency took the position that it “does not intend to consider the distribution of such medical and scientific information in accordance with the recommendations in [the] guidance as establishing intent that the product be used for an unapproved use.”¹⁶⁷ The Guidance’s more expansive approach to what is “promotional” raises legal issues that are discussed in the next subsection. Under the Guidance, the information in the distributed article must not be false or misleading, and the distribution must be accompanied by discourses about the lack of FDA approval, funding by the company for any author, and any safety concerns known to the manufacturer that are not discussed in the article.¹⁶⁸ According to an article in the *New England Journal of Medicine*, the “loosening” of restrictions on the use of reprints made by the Guidance could “present challenges for medical journals, as companies seek to ensure that their products are described favorably in articles.”¹⁶⁹ According to the article, private enforcement actions and criminal prosecutions under fraud and abuse statutes may “help fill the regulatory gap” in the absence of FDA action.¹⁷⁰

C. *Legal Issues with Basis for Reprint Guidance*

The Reprint Guidance has an ambiguous basis for its position. That position could have a legal basis or a constitutional one, or simply be an enforcement policy. All of these alternatives present difficulties.

1. *Legal Basis for Determining Intent and Promotion*

a. *Scope of Promotional Distributions*

In the Reprint Guidance, the Agency stated that it did not “intend” to regard nonpromotional distributions of nonmisleading scientific information in accordance with the Guidance to be evidence of intent that the product

166. Reprint Guidance, *supra* note 19, at 7.

167. *Id.*

168. *Id.* at 5, 7.

169. Mello et al., *supra* note 164, at 1557.

170. *Id.* at 1561–65 (reviewing prosecutions and private litigation).

be used for an unapproved purpose. The Guidance gives the illustration that a reprint could be distributed at medical conferences in connection with scientific exchanges but not in promotional settings in the exhibit halls at the conference.¹⁷¹

The Guidance failed to address, though, the significance of widespread distributions to doctors by a drug company of reprints of studies, funded by the company, of new uses of their drug as a basis for determining a promotional aim. This includes distributions of reprints that are prepackaged or involve mass mailings by the manufacturer, which can lead to a wide distribution in interstate commerce of drugs for uses that may be risky. Distributions like these can be promotional because they encourage wide off-label drug use. This factor may make the determination fact-dependent and make “as applied” review appropriate.¹⁷²

The Guidance also characterizes reprints distributed to doctors by a “sales representative” in a doctor’s office as promotional if distributed with promotional material or if accompanied by a discussion during the sales visit.¹⁷³ The clear implication is that a handout by the sales representative without comment is not promotional. This is inappropriate because the handout brings the off-label use to the physician’s attention and can suggest an endorsement by the company. The Guidance needs to be revised to provide a broader test for what is promotional.

The Guidance also fails to acknowledge adequately that in some cases the labeling provisions have been interpreted broadly to reach any material, including advertisements, that explain the purpose of the product, even if the material is not physically attached.¹⁷⁴ If the distribution were viewed as an intended promotion of the drug for an unapproved use by the company, like an advertisement to doctors, the distribution would be barred by the Agency’s advertising regulations.¹⁷⁵

171. Reprint Guidance, *supra* note 19, at 6; *see also supra* Part IV.B.

172. For merits in general of “as applied” review, see Edward A. Hartnett, *Modest Hope for a Modest Roberts Court: Deference, Facial Challenges, and the Comparative Competence of Courts*, 59 SMU L. REV. 1735 (2006).

173. *See* Reprint Guidance, *supra* note 19, at 6.

174. *Kordel v. United States*, 335 U.S. 345, 348–49 (1948). The label for the drug must also contain adequate information about all of its intended uses as determined from any relevant source. *Alberty Food Prods. v. United States*, 185 F.2d 321, 326–27 (9th Cir. 1950).

175. Prescription Drug Advertising, 21 C.F.R. § 202.1(e)(4) (2009).

b. Impact on Jurisdiction over Misleading Statements

The Agency's jurisdiction over misleading labeling for any drug depends upon a showing that the drug is "intended" to prevent or treat disease or to affect the body.¹⁷⁶ If a distribution does not constitute an intended use, the Agency would not be able to regulate misleading statements. Thus the Agency would not seem to have any jurisdiction if a sales representative distributed to a doctor, without comment, a reprint with false and misleading statements, even though the Guidance is not intended to apply to reprints with such statements.¹⁷⁷

c. Complexity of Issue

The Guidance also raises unresolved questions at the frontiers of the Agency's jurisdiction about the basis for determining "intent," "labeling," and "promotional."¹⁷⁸ That debate is dramatically illustrated by FDA's effort to regulate tobacco as a drug because of the manufacturer's knowledge of the addictive effect of nicotine on the body, the manipulation of the nicotine level, and the foreseeable consumer use for that effect.¹⁷⁹ The companies argued that intent is only established by express drug claims by the manufacturer. The Court, though, in *Brown & Williamson Tobacco Corp. v. FDA*, decided it did not need to resolve the meaning of intent because even if FDA were correct, the Agency would lose on other statutory grounds.¹⁸⁰

The Court's deliberate decision not to resolve the meaning of intent leaves the outer scope of the Agency's jurisdiction unsettled. Perhaps the Court wanted to avoid a simple resolution to a question whose consequences for the range of drug issues was not clear. The practical lesson about the complexity of the issues would seem to be the

176. 21 U.S.C. § 321(g) (2006).

177. Reprint Guidance, *supra* note 19, at 6.

178. The Guidance also fails to acknowledge adequately that, in some cases, the labeling provisions have been interpreted broadly to reach any material, including advertisements, that explain the purpose of the product even if the material is not physically attached. *See Kordel*, 355 U.S. at 348–49.

179. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 126–29 (2000). Some appellate courts have upheld a broad reading of intent, including Judge Friendly finding that "objective evidence" could establish intent in a case involving dietary supplements. *Nat'l Nutritional Foods Ass'n v. FDA*, 504 F.2d 761, 789 (2d Cir. 1974). A district court rejected "foreseeable use" as the basis for finding intent that drugs would be used off-label for pediatric use. *Ass'n of Am. Physicians v. FDA*, 226 F. Supp. 2d 204, 215–18 (D.D.C. 2002). The Agency did not appeal the decision, and Congress later provided incentives to encourage pediatric testing. *See HUTT ET AL. supra* note 52, at 642–44.

180. *Brown & Williamson*, 529 U.S. at 131–32.

desirability of looking for alternative means to address the dispute. This will be explored below after considering the other basis that may be thought to support the Reprint Guidance.

2. Reprints as Constitutionally Protected Scientific Exchanges?

The Reprint Guidance characterizes the distribution of reprints as one that relates to “medical and scientific information.”¹⁸¹ The Agency also states that it issued the Guidance in “recognition of the public health value to health care professionals of receiving truthful . . . information.”¹⁸² If the distributions were to be characterized as part of a scientific exchange, they may receive the highest constitutional protections available, like that accorded to public discussion and political speech.

Drawing the line between public discourse and commercial speech is not an easy one.¹⁸³ A relevant test, though, is to consider whether the speech is intended by the manufacturer to increase the sales of a particular product.¹⁸⁴ The test can reach a manufacturer’s distribution of reprints of articles. The characterization issue has some resemblance to the question of whether legal academics who distribute reprints of their articles to other professors are doing so to advance legal knowledge, to promote their reputation, or to do both. A dual motive, in the case of distributions by a drug company, warrants classifying the activity as commercial speech because the effect and aim can be to encourage sales of a specific product. In determining the manufacturer’s intent it would also be relevant to know the basis for the selection by the manufacturer of the reprints it chooses to distribute. For example, does the company only distribute reprints favorable to the drug that are funded by the company? The distribution may also come with some sort of cover letter that may seem like an endorsement of the new use.

181. Reprint Guidance, *supra* note 19, at 7.

182. *Id.* at 4.

183. See Symposium, *supra* note 10, at 336–42 (describing differences between Professors Chemerinsky, Shiffrin, and Sullivan on the aims of the First Amendment and its relevance in identifying the scope of commercial speech).

184. See *Bolger v. Young Drug Prods. Corp.*, 463 U.S. 60, 66–67 (1983); Symposium, *supra* note 10, at 341–42, 354–55 (citing remarks of Erwin Chemerinsky identifying the test for commercial speech).

3. Adequacy of Enforcement Policy Basis

If the Guidance reflects an enforcement position, it limits the Agency's concern with preventing deception and having disclosures and has an unduly narrow test for what is promotional. The statute, though, requires Agency approval for any new use of a drug intended by the manufacturer. The enforcement position completely ignores the Agency's broader responsibility under the statute. Although the Agency enforcement priorities are usually not judicially reviewable, review is available if the Agency adopts an express policy that is "so extreme as to amount to an abdication of its statutory responsibilities."¹⁸⁵

D. Alternative Basis for Distributions and Process for Determination

The discussion below will consider alternative bases that might justify manufacturer-distributed reprints in limited circumstances. The discussion will then turn to the potential for additional safety risks from off-label uses described in reprints and the problem of relying solely on disclosures as a safeguard. The aim is to see if there are "proportional" means to promote public safety instead of having a blanket restriction on any reprints about off-label uses. Admittedly, the effort outlined below is complicated and reflects the challenges in developing intermediate proportional approaches. The better alternative, discussed at the end of this Part, may be to improve the research incentives and the circumstances in which the Agency should be able to require the manufacturer to undertake additional studies. Although this discussion examines the circumstances in which a reprint might be considered GRAS/E, the steps are relevant for a safe harbor or other bases that may be used to justify the distribution of reprints.

1. Distributions Based on GRAS/E Potential

Medical journals might contain a high-quality study on an off-label use that is similar to an adequate and well-controlled study of the type needed for approval of a NDA. The study may be so good that experts in the field might accept that the off-label use is one that could become GRAS/E. By definition a drug is not a new drug if it is GRAS/E.¹⁸⁶ General

185. Heckler v. Chaney, 470 U.S. 821, 833 n.4 (1985). *But see* Young v. Cmty. Nutrition Inst., 476 U.S. 974, 981–82 (1986) (deferring to the Agency's interpretation of a dangling participle).

186. 21 U.S.C. § 321(p) (2006).

recognition depends, though, on adequate studies that have the same quality and quantity as those needed for approval of a new drug.¹⁸⁷ A drug new to the market cannot have the experience by experts needed for general recognition. On the other hand, when an approved drug is on the market, experts, as well as doctors, can become familiar with its other uses, including those in medical journals. In unusual cases, the experience of experts combined with high-quality studies might be sufficient to make the new off-label use GRAS/E.¹⁸⁸ If a reprint has that degree of general recognition, a manufacturer would seem to be able to distribute it without Agency approval. The Agency would still have jurisdiction over the drug with respect to misleading labeling or promotions.

General recognition is virtually impossible to exist, though, for a newly published journal article. It takes time for experts to read and assess an article and come to a general acceptance. Moreover, off-label uses can have unexpected postmarket risks. When the Agency believes an article about an off-label use is in the zone of potentially being GRAS/E, the Agency might exercise its enforcement discretion and rely on disclosures, if they are adequate, rather than to test how close the off-label use has come to being generally recognized.

2. Adequate Disclosures and Agency Review

In this setting, adequate disclosures by the company are especially needed to avoid misleading impressions about matters that can affect the assessment of the reliability of the study that relate to patient safety and whether experts would recognize the new use as GRAS/E.¹⁸⁹ The discussion below will deal with the process for Agency review of disclosures and the

187. *Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609, 629 (1973) (finding that “general recognition” depends upon the same quantity and quality of scientific evidence needed for approval of an NDA); 21 C.F.R. § 310.3(h) (2009). The Court recognized that “in some cases” recognition “might be made” without that level of support, but the reach of the inquiry is the same. *Weinberger v. Bentelex Pharm., Inc.*, 412 U.S. 645, 652–53 (1973).

188. The labeling approved for use of over-the-counter aspirin in reducing the risk of Transient Ischemic Attacks provides an illustration of a drug that became GRAS/E for a new use based on published studies without having an approved new drug application for the use. *See* Background and Final Rule, 63 Fed. Reg. 56,802 (Oct. 23, 1998).

189. In judging whether a matter is misleading, material omissions are considered. 21 U.S.C. § 321(n) (2006).

need for more studies when drug companies distribute reprints on off-label uses on such a basis.

3. Disclosures and Prior Review

The determination about the need for disclosures and additional studies is appropriately made before the reprint is distributed. Prior review is constitutionally suspect, but the Court has stated that it may be more acceptable for commercial speech because it is “hardier.”¹⁹⁰ Prior review by the Agency of the distribution planned by the company is needed because experts, as well as doctors, cannot have enough familiarity with a newly published article to permit general recognition. The Agency may appropriately use its enforcement discretion if the reprinted article may win general recognition. Until that occurs, though, prior review provides a safeguard to ensure that there are nonmisleading disclosures.

As a result of the review, the Agency might then request the manufacturer to provide more disclosures with the distributed the reprint. If the company failed to do so, the Agency may find the distribution misleading and take enforcement action or pursue other measures. If the distribution planned by the manufacturer is misleading, commercial speech does not protect it. The discussion below will deal with the types of disclosures that may be needed and will then examine whether the Constitution will allow the Agency to require more studies in case the Agency believes that disclosures are not enough. The Agency may also reexamine the intended use of the drug in light of the distribution.

4. Disclosures on Factors that Affect Assessment of Reliability

Under this approach, the manufacturer should have the responsibility for making adequate disclosures in the accompanying statement of any matters that affect the assessment of the reliability or independence of the study. The disclosures should cover matters like those noted below.

a. Disclosures on Funding of Authors, “Ghostwriting,” and Conflicts of Interest

The Reprint Guidance calls for drug companies that distributed reprints to disclose in an accompanying statement any compensation made to an “author” of a study, whether credited or not, who meets the standards

190. See *Ctr. Hudson Gas & Elec. Corp. v. Public Serv. Comm’n*, 447 U.S. 557, 564 n.6, 571 n.13 (1980).

for authorship.¹⁹¹ This disclosure will provide help in understanding the potential for conflict of interest. Moreover, it helps in dealing with “ghostwriting” of medical articles, which has emerged as a major concern. Recently, a company was reported to have hired a ghostwriter to write articles favorable to a drug and then to help submit the article to a target journal.¹⁹² A newspaper article also reported that the “[s]cientific integrity of medical research has been clouded in recent years by articles that were drafted by drug company-sponsored ghostwriters and then passed off as the work of independent academic writers.”¹⁹³

Under the Pharmaceutical Research and Manufacturers of America’s (PhRMA) recently revised *Principles on Clinical Trials*, the author has the responsibility for identifying in the journal article any individuals who provided assistance and the funding source.¹⁹⁴ The author is also to disclose the role, if any, of the study sponsor in study design, interpretation of data, and writing of the report.¹⁹⁵ These matters are so important that the drug sponsor who distributes a reprint should disclose in the accompanying statement any role of the sponsor in design, interpretation, and writing of the study. Any funding of contributors to an article should also be disclosed even though their role is less than that of an author.¹⁹⁶ These disclosures are needed in the accompanying statement, even if they are also given in the article because of the manufacturer’s role in distributing the reprint to a wider audience. When the manufacturer distributes a reprint, the company has the responsibility to be sure the author’s disclosures are adequate with respect to any matter known to the manufacturer.

191. Reprint Guidance, *supra* note 19, at 7 & n.8.

192. See Natasha Singer, *Medical Papers by Ghostwriters Pushed Therapy*, N.Y. TIMES, Aug. 5, 2009, at A1; Letter from Senator Charles E. Grassley to Raynard S. Kington, Acting Dir., Nat’l Inst. Health, Aug. 11, 2009, available at <http://www.npr.org/assets/blogs/health/images/2009/08/nihletter.pdf>.

193. Natasha Singer & Duff Wilson, *Unmasking the Ghosts: Medical Editors Take On Hidden Writers*, N.Y. TIMES, Sept. 18, 2009, at B1. Some journals are barring ghostwriting for opinion pieces. *Id.*

194. PHARM. RESEARCH & MFG. AM., PRINCIPLES ON CONDUCT OF CLINICAL TRIALS 17 (2009), available at http://www.phrma.org/files/attachments/042009_Clinical%20Trial%20Principles_FINAL.pdf.

195. *Id.*

196. *Id.* The Reprint Guidance calls for disclosures of the funding by the company for “any author.” See Reprint Guidance, *supra* note 19, at 7.

b. Conflicts of Interest and Difference from Agency Role

The disclosure requirements for journal authors highlight a key difference between medical journal writers and the FDA role. FDA reviewers cannot have conflicts of interest. Medical article writers can have conflicts so long as they are disclosed. As the industry recognizes, in the “strict sense, some conflict of interest may exist in all research settings,” but there may only be a limited number of physicians who are “best qualified” to enroll sufficient patients in a study.¹⁹⁷

c. Access to Database for Off-Label Uses

FDA reviewers have access to the full database for a study when FDA approval is sought. The Agency can examine the database to make an independent statistical analysis. That review may spot risk signals as it did in the case of Vioxx.¹⁹⁸ In the case of an off-label use described in a medical article, the Agency does not have that access because the Agency’s approval has not been sought.

The investigators and journal reviewers, though, may have a more limited access to the data about the study than FDA would have. The database “is owned by the sponsor,” and intellectual property protections are considered in making disclosures.¹⁹⁹ Under the 2009 standards, a sponsor will “seek” to provide “meaningful access” to investigators of clinical data for multiclinic trials, and “authors” will be given all data “needed” to support publication.²⁰⁰ The drug sponsor will provide a “synopsis of the clinical trial protocol” when requested by a medical journal that is reviewing a submitted manuscript “with the understanding that such documents are confidential and should be returned to the sponsor.”²⁰¹

d. Access by Blind Reviewers

Medical journals use “blind reviewers” to perform a role that seems similar in some respects to that of the Agency. It is not clear, though, how much blind reviewers examine the full database and whether they

197. PHARM. RESEARCH & MFG. AM., *supra* note 194, at 16.

198. See *supra* Part III for the scope of the medical review for Vioxx.

199. PHARM. RESEARCH & MFG. AM., *supra* note 194, at 19. In 2002, the drug companies stated that as owners of the database they have “discretion” in providing access, and in general, “study databases are only made available to regulatory authorities.” See Margaret Gilhooley, *Drug Regulation and the Constitution After Western States*, 37 U. RICH. L. REV. 901, 923–25 & n.126 (2003); see *supra* Part V.D.3.a.

200. PHARM. RESEARCH & MFG. AM., *supra* note 194, at 19.

201. See *id.* at 24–25.

would be able to obtain access if they sought it. Without that type of independent review, the journal articles on off-label uses do not have the same double-check on the validity of the study that comes from the Agency's review of an approved use. Although these matters involve matters of scientific research judgment, consideration seems needed of a disclosure on the extent to which the blind reviewers and other medical journal reviewers and investigators sought and obtained the full database in order to do an independent analysis.

e. Difference Between Criteria for Medical Journals and Distributions

Medical journal editors rightly use their scientific and editorial judgment in determining the criteria for publication. The evaluation of the adequacy of the article in journals is not a matter for government decision. The disclosures that authors should make in the journal are also ones for the journal, not the Agency, to decide.

On the other hand, if the drug sponsor distributes reprints of an article to doctors, the distribution goes beyond being an exchange of scientific information, and as discussed above, it has a promotional aspect because of the effect it can have in increasing sales for a particular product. When distributing a reprint, the sponsor should make disclosures in the accompanying statement about funding, any role in study design and writing, and the limits on access to data as discussed above. That information seems especially relevant for doctors to consider in evaluating a use with a wide health impact. Moreover, it seems a relevant consideration for the Agency to take into account in determining whether the study is GRAS/E and whether additional evaluation or studies are needed.

E. Need for Additional Testing

As discussed below, disclosures may not be enough to protect the public or to provide a potential basis for finding that the use may be one that is or could become GRAS/E. The Agency should be able to call for more testing and in appropriate circumstances, provide for its being done while the reprint is being distributed.

1. Potential Safety Issues

Medical articles on off-label uses can involve important risk not dealt with in the initial approval. For example, suppose a drug was approved for short-term pain relief. Later, a medical study funded by the drug company and distributed to doctors reports that the drug can reduce the incidence of heart attacks when taken on a continuing basis at a higher dose by those at risk. The new use is for chronic, rather than short-term, use and at a higher dose. Moreover, if the drug does not work to reduce heart attacks, it can have indirect safety consequences by diverting the doctor from using another treatment that might be available. These differences could lead to significant safety harm. The new use would also not likely be one that has sufficient use to be GRAS/E in these circumstances. Moreover, the experience with Vioxx has illustrated the potential for postapproval risks from any drug.²⁰² That potential warrants additional surveillance and, in some cases, additional testing.

2. Additional Testing and Supplemental New Drug Application, Timing, and Disclosures

The Agency should be able, when needed, to require the manufacturer to undertake additional testing when the manufacturer has initiated distributions and important unresolved safety questions exist about the safety of the new use or its effectiveness. In determining whether there is a specific need, the Agency should take into account the disclosures suggested above that can affect the reliability of the study. For example, if the study is largely written by nonacademic contributors, with funding from the company, the Agency clearly may seek to have the company file a supplemental application to enable the Agency to call for confirmatory testing needed to substantiate the findings. That testing might be done after the distribution of the article. Congress provided for that alternative earlier, and it still provides a model on the options for the timing of the testing.²⁰³

202. See *supra* Part III.A (summarizing the IOM's recommendation on the need for improved postmarket surveillance and changes in the Agency's authority); *supra* Part III.B (describing the cardiovascular risks found after approval); see also *supra* Part III for a discussion of Vioxx.

203. 21 U.S.C. § 360aaa-3(d)(2) (Supp. III 1994) (expired pursuant to Pub. L. No. 105-115, 111 Stat. 2364 (1997), and 63 Fed. Reg. 64,556 (Nov. 20, 1998)).

3. Postmarket Surveillance

If the manufacturer is distributing reprints about off-label uses that encourage wide use, provision should be made for postmarket surveillance and testing for the unexpected risks the drug may pose. The need is similar to that for newly approved drugs.

F. Commercial Speech Restraints

If the Agency were to seek to have a company submit a supplemental NDA to do additional studies, a constitutional challenge may occur. Under *Western States*, these measures may be considered more restrictive than necessary because a disclosure to the doctor about the lack of studies on the issue would be sufficient. When the questions about the support for the study involve safety risks to a large number of patients, though, Congress and the Agency should be able to decide that more protection of the public is needed. If, for example, the company distributes a study about the stroke prevention benefit of a pain pill at a high dose, the Agency might be concerned if the study in the medical article is poorly controlled or has been ghostwritten or had a short duration. The wide use of the article based on the reprint distributed by the company could create a large risk. Although a disclosure with the reprint about the problems may affect prescribing habits that should not be the only remedy available, the need to prevent harm to the public should be given its due weight.

G. A Better Alternative: Research Incentives for FDA-Approved Research and Improved Postapproval-Risk Tracking

1. Limited Incentive

Manufacturers have been concerned with the lack of research incentives to do additional research on their approved drug. The law already gives the brand manufacturer three years of market exclusivity for research when FDA approves a supplemental NDA for the new use for the drug.²⁰⁴ The economic benefit, however, is limited. Once the patent and other exclusivity periods expire on the original use of the brand drug, the generic drug can be marketed for the primary use.

204. 21 U.S.C. § 355(j)(D)(iv) (2006).

Although the generic drug cannot make any claim for the supplemental use, doctors can prescribe the drug for the additional use, and some states and insurance companies might even require generic substitution.²⁰⁵ A court rejected the argument of a drug company that the research exclusivity should preclude any generic availability until the end of the three-year period of exclusivity.²⁰⁶

The limited incentives at present for additional research on a marketed drug may provide an added reason for manufacturers to believe in the importance of commercial speech protections. If they had a more meaningful research incentives, perhaps they might seek to get a new use approved as a supplemental use rather than distribute medical journal articles they fund about off-label uses. In some settings, Congress has recognized the relevance of the lack of market incentives in determining what studies companies should be expected to do on off-label uses.²⁰⁷

2. *Improving Reporting and Risk Identification for Off-Label Uses*

Providing incentives for obtaining FDA approval of an off-label use may also provide a better means of monitoring the risks from off-label uses. The testing for approved drugs is not adequate to detect all risks that may occur in use, as discussed above. Similar issues may well arise with new off-label uses reported in medical journals, and especially so if the new use is for a more serious condition or a longer duration of use than that for which the initial approval was obtained.

The way that the risks from off-label uses are reported on the drug label needs further examination. Under FDA's regulations, the physician drug labeling needs to be revised to "[i]nclude a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; [however] a causal association need not have been definitively established."²⁰⁸

Although risks from off-label uses can be reflected in the warnings, the statement is not to be "promotional."²⁰⁹ It may be difficult, though, to identify fully the risks from a specific off-label use without seeming

205. Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1496 (D.C. Cir. 1996).

206. *Id.* at 1500; *see* NOAH, *supra* note 151, at 869–70; Eisenberg, *supra* note 150, at 482.

207. 21 U.S.C. § 360aaa-3(d)(2) (expired). Congress provided that the Agency could exempt a company from having to do an additional study when the company distributed reprints on an off-label use if the studies were "economically prohibitive" taking into account factors such as the lack of availability of exclusive marketing.

208. 21 C.F.R. § 201.57 (2009).

209. *Allergan Government Reply*, *supra* note 21.

to recognize or encourage the use. Without a more specific description, doctors may not have an optimal basis to evaluate whether an off-label use described in reprints continues to be warranted in light of emerging risks.

The difficulties, though, go deeper. There does not seem to be any special provision for postmarket surveillance of new off-label uses. The manufacturer does not seem to be obliged to pay “user fees” to track risks from off-label uses that are described in reprints distributed by the company. If the off-label use leads to new risks, there does not seem to be any expectation at present that the manufacturer who distributed the journal article will inform recipients of the additional risks.

3. Possible Scope of Incentive

Given these difficulties, consideration is needed to giving the drug manufacturer an incentive to obtain approval from the Agency for sound research on off-label uses. One approach is for Congress to provide a strong three-year exclusivity period for adequate studies to support a new use, without blocking the generic availability of the drug for its primary original use when the patent for the original use ends.²¹⁰ Perhaps it might be possible to do so while encouraging better postmarket-risk reporting for the new use. To return to the example given above, suppose a drug has been approved for pain and the manufacturer submits a supplemental NDA to FDA based on medical studies for a benefit in stroke prevention from the drug. If FDA approved the new use, the expanded use might receive a special designation such as having an “S-P” designation added to the name to indicate the particular use, and the pill might be given a different color or form.²¹¹ Doing so should permit better identification of the side effects and risks from the supplemental use.

Although it might not be possible to stop doctors from substituting the generic for the new form of the drug, the aim would be to discourage them from doing so in order to better monitor the new risk and to preserve the value of the research incentive provided. Insurance reimbursement should be based on whether a code for a stroke risk was designated as the reason for

210. See Part V.G.1 for difficulties with present incentive.

211. An analogy is provided to the exclusivity protections for prescription drugs when they become over-the-counter. See Gilhooley, *supra* note 51, at 29 & n.146 (noting exclusivity against generic OTC products for Prilosec OTC).

the doctor visit and the prescription because that designation promotes a better understanding of the risk from the new use.²¹²

There is a risk, of course, that a drug company might first distribute reprints about off-label uses and later submit a supplemental NDA to substantiate the benefit and obtain the added economic incentives for the research. This creates a tension with the aim of providing the expanded incentive because the weaknesses in determining the risks from the off-label uses will occur when it is based on the distributed reprint. Perhaps the period of added exclusivity should be reduced if the company does not submit the supplemental NDA to do the confirmatory research at the time the company initiates distribution of reprints.

VI. CONCLUSION

Prescription drugs carry considerable risks, and this factor should carry special weight in assessing whether the constitutional protections for commercial speech permit speech restrictions. The best approach might be to revise the commercial speech test to recognize the importance of the protection of the public health as a separate prong. The alternative is to endorse the test stated in the dissent in *Western States*. That test takes account of the “proportionality” between the possible risk and the aim and duration of the restriction. This paper explores how that test might work in the areas in which there has been debate and criticism of the application of commercial speech to drug regulation. Although the safety-focused proportionality test has uncertainties and presents challenges for the Agency, it holds the promise for greater public protection.

The paper suggests that a moratorium on DTC advertising for drugs should be permissible under the proportionality test for important categories of drugs, including those with specific risk factors. These include advertisements for drugs for which risk signals have been found, those in a new therapeutic class, or for use by patients at special risk, such as those with a serious acute condition. In addition, a moratorium seems warranted in the interest of protecting the public health when scientists believe there is substantial uncertainty about the potential for added risk from a drug that will be widely used.²¹³ The potential for additional safety risks for drugs like these seems sufficient to warrant a delay in the consumer advertisements. That delay in advertisements

212. A different outcome seems warranted if the doctor entered a do-not-substitute order or its equivalent.

213. See 21 U.S.C. § 355(o)(3) (Supp. I 2006) for criteria under which the Agency may require postapproval studies.

permits doctors to learn about the extent of the risks from postmarket surveillance as well as their experience before general promotion to the public starts. If the Agency believes that the DTC advertisements pose a potential significant potential safety risk to the general public, the Agency should seek to have a moratorium. A direct test is warranted on the scope of the protections for commercial speech when that speech may adversely affect the public health.

The other focus of the paper is on company-initiated distributions to doctors of reprints of medical articles about a study of a new off-label use of an approved drug. The distribution of the reprint can encourage the new use by making it more widely known to doctors and by seeming to have the endorsement of the company. In the past the Agency regarded many company-initiated distributions as subject to the drug approval requirements, but a lower court found those distributions to be constitutionally protected in a decision that was vacated on other grounds.²¹⁴ The Reprint Guidance issued at the end of the Bush administration took the position that the Agency did not intend to regard “nonpromotional” distributions by the company about nonmisleading studies as providing evidence of an intended use of the drug.²¹⁵ The distribution, though, must be nonmisleading and disclose safety risks that are not discussed in the article but are known to the manufacturer. This paper examines the statutory and policy difficulties with the Bush Guidance, and some alternatives that might be considered.²¹⁶ The Obama administration has now accepted that conduct outlined in the Reprint Guidance “is not unlawful” in the context of the *Allergan* case.²¹⁷ The Reprint Guidance, though, has an unduly narrow approach for determining what is “promotional,” and therefore it needs to be revised.

This Article explores alternatives to identify when distributing reprints on off-label uses should be considered acceptable by building on

214. See *supra* Part V.A; see also *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000); *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999).

215. See Reprint Guidance, *supra* note 19; see *supra* Part V.B.

216. The discussion in Part V.D also explores an alternative basis that might warrant, in limited circumstances, the manufacturer’s distribution of medical articles when the use described in this Article may be generally recognized by experts as safe and effective. The need to improve the research incentives for better testing is also explored.

217. *Allergan* Government Reply, *supra* note 21, at 9.

alternatives that Congress accepted in the past.²¹⁸ As discussed in Part V.D, if a manufacturer distributes reprints, at a minimum adequate disclosures are needed with an opportunity for agency review. A disclosure of information that can affect the assessment of the reliability of the study should accompany the reprint. This should include any role of the company in the interpretation of the study and in the funding of authors, contributors, or “ghostwriters.” A disclosure also seems needed on the extent to which the study investigators and medical journal reviewers sought and obtained the full database in order to do an independent analysis. FDA should also be able to consider factors like these to determine that disclosures are not sufficient to guard against a significant safety risk and that the drug manufacturer needs to submit a supplemental NDA to undertake additional research. Constitutional issues may be raised, though, if the Agency or Congress called for the drug manufacturer to do additional studies under a supplemental NDA.²¹⁹ The drug approval system, though, is not fundamentally one of providing nondeceptive information. Prior approval by the Agency of the safety and efficacy of a drug is required before a new drug can be sold. As the D.C. Circuit found in *Abigail Alliance*,²²⁰ an unapproved drug cannot constitutionally be sold, even to cancer patients, under the due process clause, simply with a disclosure about the lack of FDA approval or the lack of studies. Doing so would undercut Congress’s legitimate concern with public safety, and it could undercut the testing system because few may volunteer for controlled testing if they can get the hoped-for cure—based on disclosures—without having to participate in a real test.

Similar concerns arise with respect to off-label uses. The scope of the risk and benefit to the patients is best determined by controlled tests with an independent review by the Agency. The manufacturer’s wide distribution of these reprints is appropriately seen as being intended to promote the off-label use and increase the sales of a particular product, and thus to be commercial speech,²²¹ rather than simply an effort to advance a scientific exchange of ideas. If drug companies can readily distribute medical articles about off-label uses to doctors with simple

218. See 21 U.S.C. § 360aaa-6(b) (Supp. III 1994) (expired pursuant to Pub. L. No. 105-115, 111 Stat. 2364 (1997), and 63 Fed. Reg. 64,556 (Nov. 20, 1998)); see also *supra* Part V.A.

219. See *Henney*, 56 F. Supp. 2d 81; *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998).

220. *Abigail Alliance for Better Access to Developmental Drugs v. Eschenbach*, 495 F.3d 695, 703–06 (D.C. Cir. 2007).

221. See *Bolger v. Young Drug Prods. Corp.*, 463 U.S. 60, 65–68 (1983); Symposium, *supra* note 10, at 341–42, 354 (citing comments of Professor Chemerinsky).

disclosures about the lack of agency approval, the company may seek Agency approval for the easiest use to support, such as ordinary pain relief. The more significant uses the drug may have, at a higher dose, with a closer risk-benefit balance may be the subject of medical articles that the company funds and distributes with disclosures about the lack of agency approval. The FDA approval system will become a mere preliminary.²²²

Some may doubt that the Court will be willing to lessen the rigor of commercial speech doctrine. The Court's recent decision in *Wyeth v. Levine*, though, recognizes the importance of drug safety and that the drug maker has the "primary responsibility" to revise drug labeling to reflect new emerging risks when needed.²²³ Under *Wyeth*, tort liability is not preempted unless there is "clear evidence" that the FDA would have rejected a new warning, which is not shown when the Agency gave no more than "passing attention" to the matter.²²⁴ A DTC moratorium gives doctors and the Agency the opportunity to give more than "passing attention" to the significance of an emerging safety risk before consumers are influenced by DTC advertisements to request a drug or pressure their doctors to prescribe it. Even if *Wyeth* is not read that broadly, the safety risks that prescription drugs pose deserve more weight under the commercial speech test.

Decisions about the "best way to protect the health and safety of the American public" rightly belong to Congress, as the dissent in *Western States* pointed out. An "overly rigid" commercial speech doctrine could repeat the mistakes of the experience with substantive due process.²²⁵ If Congress is more restrictive than the public wants, the electorate can seek change. The Court should be hesitant about putting drug safety decisions beyond the reach of the elected branches of the government.

222. See Mello et al., *supra* note 164, at 1563.

223. *Wyeth v. Levine*, 129 S. Ct. 1187, 1197–98 (2009).

224. *Id.* at 1198–99.

225. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 389 (Breyer, J., dissenting); see *supra* Part IV.B.2.e.

