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ADDRESSING POTENTIAL DRUG RISKS: 
THE LIMITS OF TESTING, RISK SIGNALS, PREEMPTION, AND THE DRUG REFORM LEGISLATION*

MARGARET GILHOOLEY**

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1. INTRODUCTION

The cardiovascular safety risks posed by Vioxx, which were found in tests after
the drug was placed on the market, created public concerns about both a drug’s
potential risks even following approval by the Food and Drug Administration
(FDA)¹ and the existence of risks without labeling to alert the patient’s doctor.²
After Vioxx was voluntarily withdrawn, the drug sponsor was sued and found liable
in several products liability cases, based partly on documents showing that the
company’s employees were aware of cardiovascular risk signals disclosed neither

1. Before a new drug can be marketed, the FDA must approve the drug as safe and effective. See
21 U.S.C. § 355(d) (2000) (providing the grounds for which the FDA may refuse an application for drug
approval).
2. See Becky Bright, Americans Growing Less Confident in FDA’s Job on Safety, Poll Shows,
(reporting that 36% of those polled in 2006 thought “the agency does a good or excellent job,” while
in 2004 56% felt that the agency “did a good or excellent job in [ensuring the] safety and efficacy of
new prescription drugs”); Gardiner Harris, F.D.A. Responds to Criticism with New Caution, N.Y.
TIMES, Aug. 6, 2005, at A1, A11 (reporting that “[t]he agency once avoided issuing disturbing warnings
about drugs unless studies proved that a risk was certain” but that “[t]he Vioxx withdrawal has been a driving
force for [change] at the agency”). Members of Congress have criticized the FDA, stating that “[w]hen
[the] FDA goes through a 14-month-long period to get a labeling change that both it and its panel of
experts agree is necessary, that shows us that something is wrong.” Agriculture, Rural Development,
Food and Drug Administration, and Related Agencies Appropriations for 2006: Hearings Before a
Member, House Comm. on Appropriations).
to the agency nor to physicians in the drug’s labeling. Concerns with the safety of drugs such as Vioxx led the FDA to request a study by the Institute of Medicine of the National Academies (IOM) on the Future of Drug Safety (IOM Report). The report adopted a “vision of a transformed drug safety system” that “has at its core a lifecycle approach to drug risk and benefit.”

The recently enacted Food and Drug Administration Amendments Act of 2007 (FDAA) renewed the user fees needed to fund a major part of the FDA’s drug program and built on the IOM’s recommendation to adopt a risk management approach to drug risks. The new law makes significant changes to drug regulation in a number of ways, including authorizing restrictions on the availability of prescription drugs to doctors who have special training when those restrictions are needed to ensure safe use of drugs with “known serious risks.” The focus here is on the legislative changes that deal most directly with the safety issues raised by Vioxx. These changes present a mixed picture. The agency will now have express authority to require additional postmarket tests and new warnings, but the agency


4. INST. OF MED. OF THE NAT’L ACADEMIES, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE PUBLIC HEALTH (Alina Baciu, Kathleen Stratton & Sheila P. Burke eds., 2006) [hereinafter IOM REPORT]; see U.S. FOOD & DRUG ADMIN., STRENGTHENING DRUG SAFETY (2007), available at http://www.fda.gov/consumer/features/drugsafety0607.pdf. Recommendations like those made by the IOM can be seen as an extension of systems analysis to the area of drug use as a way to reduce harm, an approach that has become important in other areas of health care. See generally INST. OF MED., TO ERR IS HUMAN: BUILDING A SAFER HEALTH SYSTEM 17 (Linda T. Kohn, Janet M. Corrigan & Molla S. Donaldson eds., 2000) (proposing “a comprehensive approach for reducing medical errors and improving patient safety . . . [by employing] market and regulatory strategies, public and private strategies, and strategies that are implemented inside health care organizations as well as in their external environment”).

5. IOM REPORT, supra note 4, at 4.

6. Pub. L. No. 110-85, 121 Stat. 823 (2007) (designating renewed user fees). While the FDAA has delayed effective dates for some of its provisions, this factor is not discussed here. The statute grants authority to implement the new law to the Secretary of Health and Human Services, and the Secretary has redelegated this authority to the Commissioner of Food and Drugs. See U.S. FOOD & DRUG ADMIN., FDA STAFF MANUAL GUIDE, VOLUME II—DELEGATIONS OF AUTHORITY § 1410.10 (2007), available at http://www.fda.gov/smg/vol2/1410/1410_10.html. In light of this delegation, this Article refers to the FDA or the agency in implementing the law.

7. Sec. 103, § 736(a), 121 Stat. at 826 (to be codified at 21 U.S.C. § 379h(a)).

8. Sec. 901(b), § 505, 121 Stat. at 923 (to be codified at 21 U.S.C. § 355-1(f)(3)); see IOM REPORT, supra note 4, at 119–21 (discussing the model for risk management restrictions provided by those used for Accutane).

9. See. 901(a), § 505, 121 Stat. at 923 (to be codified 21 U.S.C. 355(o)(1), (3), (4)); see infra notes 122–24 and accompanying text.
will have to issue regulations and guidance to establish the dispute resolution procedures needed to implement the authority, a process that could take years. The agency will be able to impose fines if the sponsor fails to comply with agency requirements for new tests and warnings. Drug companies will also pay user fees that will fund an active surveillance system to uncover postmarket drug risks. Drug companies have generally supported such fees, notwithstanding the cost to them, in order to avoid the delay that would occur in obtaining approval of new drugs if the FDA were to have fewer reviewers.

The first aim of this Article is to survey the changes in the FDA’s authority and to identify ways in which the authority should be implemented to address drug safety risks. As an initial step, the FDA should consider whether the standards for clinical testing for chronic use drugs like Vioxx should include more comprehensive studies or outcome testing, even if the studies are done postmarket. Providing adequate disclosures that reflect the limits of the testing done for drugs is also key. These disclosures should reflect the limited safety information provided by approvals based on surrogate endpoints, undertakings to do new postmarket studies or surveillance, and the significance of the failure to complete postmarket studies. While disclosures can be made on the new agency web site to establish postmarket safety information (Safety Information Web Site), important ones should be in the physician labeling. If the drugs will be advertised, adequate disclosures should be made in consumer advertisements about the risks of newly-approved drugs. However, Congress has not required restrictions similar to the ones recommended by the IOM Report and has simply called for a report on the use of a symbol on the drug labeling. Another initiative the FDA should undertake to

10. Sec. 901(a), § 505, 121 Stat. at 923 (to be codified at 21 U.S.C. § 355(o)(3)(f), (o)(4)(F)).
12. Sec. 902(b), § 303(f), 121 Stat. at 943 (to be codified at 21 U.S.C. § 333(f)(4)(A)).
13. Sec. 901(a), § 505, 121 Stat. at 922 (to be codified at 21 U.S.C. § 355(o)(3)).
15. Sec. 905(a), § 505(k), 121 Stat. at 944 (to be codified at 21 U.S.C. § 355(k)(3)(c)); see discussion infra Part IV.A.
17. See discussion infra Part V.A–C. Surrogate endpoints are “physiological or biochemical markers that can be . . . quickly and easily measured,” and are “predictive of important clinical outcomes.” Bandolier, Surrogate Endpoints, http://www.jr2.ox.ac.uk/bandolier/booth/glossary/surrog.html (last visited Nov. 8, 2007).
18. Sec. 915, § 505, 121 Stat. at 957 (to be codified at 21 U.S.C. § 355(r)); see discussion infra Part V.D.
19. IOM REPORT, supra note 4, at 171.
20. § 904, 121 Stat. at 944. See Part V.F.
ensure that consumers are informed about the risks from advertised drugs is to prohibit the use of reminder advertisements to consumers.\(^{21}\)

The new law will provide access via an FDA web site to summaries of “any critical issues and disagreements” concerning the approval by all reviewers, along with the agency’s response, once a drug is approved.\(^{22}\) On the other hand, no provision is made for the disclosure of risk signals found in clinical studies for new uses of marketed drugs that are still under review, the very situation that occurred with Vioxx.\(^{23}\) This Article recommends that there be a disclosure on the agency’s web site within a limited period when such risk signals are discovered in studies of new uses of marketed drugs that are still under agency review.\(^{24}\) Required disclosure in these situations could prompt a faster resolution of an important pending issue.

This Article recognizes the different positions on whether disclosure about risk signals and pending reviews is appropriate. One position endorses the authoritative expert model under which the FDA is the gatekeeper for disclosures, deciding the content of the disclosure on the labeling based on an exercise of discretion. One strength of this model is its recognition of the special expertise the FDA possesses in evaluating risks that involve complex scientific information. This expertise is based on reports from the FDA’s staff of medical reviewers and its special access to the raw data for clinical studies. This model also protects against the risk that doctors or their patients will stop using a drug with benefits out of concern about a drug’s unsubstantiated risks. Two major weaknesses of the authoritative expert model are the judgmental quality involved in assessing the drug in the face of uncertainty and the potential for extended negotiations with the drug sponsor.\(^{25}\) This Article explores a second model for disclosure, referred to as the access model, which would supplement the traditional model in the case of notable risk signals such as those found in medical reviews of clinical studies. An access model is also helpful regarding disclosures about the limits of testing and follow-up monitoring.

The other major aim of this Article is to urge reconsideration of the FDA’s recent statement of its preemption policy,\(^{26}\) a policy that would preclude imposition of liability not only when a warning addresses a specific risk, but also when there is a failure to provide warnings “the substance of which had been proposed” to the agency but had not been required by the agency.\(^{27}\) The FDA has emphasized its role as an authoritative expert, as opposed to lay jurors, in deciding on the need for warnings, as well as the need to avoid exaggeration of a risk that could “discourage

\(^{21}\) See discussion infra Part V.F.4.

\(^{22}\) See 916, § 505(1), 121 Stat. at 959 (to be codified at 21 U.S.C. § 355(I)(2)(C)(iii)).

\(^{23}\) See discussion infra Part II.B.2.

\(^{24}\) See discussion infra Part V.E.1.

\(^{25}\) This latter point is illustrated by the history of Vioxx. See Harris supra note 2; see also discussion infra Part II.B.3.

\(^{26}\) Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,921, 3,933–36 (Jan. 24, 2006) [hereinafter Preemption Statement]; see discussion infra Part VI.

\(^{27}\) Preemption Statement, supra note 26, at 3,936.
appropriate use of a beneficial drug."\(^{28}\) This position is likely to receive more attention in connection with the Supreme Court’s consideration of cases that raise different aspects of preemption regarding FDA-regulated products.\(^{29}\)

This Article examines the FDA’s Preemption Statement from a policy perspective and recommends that it be withdrawn because it fails to provide accountability for agency inaction. Under the statement, silence by the agency with respect to an undisclosed matter that has been “proposed,” perhaps only orally, could preclude a tort suit.\(^{30}\) The difficulties with the Statement are illustrated by considering how it would have applied during the negotiations over the need for a warning about the risks from Vioxx. The agency’s policy also fails to provide any access to information about pending issues or the agency’s resolution of the matter. Moreover, the policy does not reinforce the responsibility that a drug’s sponsor should have for providing information about the extent of the risk.

Still, as the FDA has noted in its Preemption Statement, the litigation process may encourage warnings that the agency may deem unwarranted.\(^{31}\) Drug sponsors may also be uncertain about the need for a warning or its form. Products liability suits are a less-than-ideal vehicle for determining what type of warning is needed and involve a retrospective determination that the drug sponsor did not do enough. The agency should adopt a new procedure that sponsors can use when they seek a definitive determination on whether a warning is needed. Unlike the agency’s present preemption policy, though, the new procedure would provide for publicly available information about the request, the risk information to support it, and the agency’s response. Under this approach, as an alternative to the present process,\(^{32}\) the sponsor could petition the agency to determine with preemptive effect whether a warning is needed about new risk information (Disclosure Determination Petition).\(^{33}\) The sponsor would have to support the petition with the type of information the agency identifies as needed to evaluate the scope of the risk. After a limited period of time, the agency would disclose on the agency web site for the drug that the petition was “under review,” thus giving notice of the ongoing evaluation of the risk signal.\(^{34}\) This Disclosure Determination Petition process may have another advantage because it may make it easier for the agency to obtain better warnings without having to utilize the new statutory authority with its unsettled

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28. *Id.* at 3,935.

29. Desiano v. Warner-Lambert & Co., 467 F.3d 85 (2d Cir. 2007) (finding that tort liability was not precluded by a claim that the sponsor committed fraud), *cert. granted sub nom.* Warner-Lambert Co. v. Kent, 128 S. Ct. 31 (Sept. 25, 2007) (No. 06-1498); Levine v. Wyeth, No. 2004-384, 2006 WL 3041078, at ¶6 (Vt. Oct. 27, 2006) (finding that the FDA labeling set a “floor, not a ceiling” and was nonpreemptive), *petition for cert. filed,* 127 S. Ct. 2451 (May 21, 2007) (No. 06-1249) (requesting the Solicitor General’s views on granting certiorari); Riegel v. Medtronic, Inc., 451 F.3d 104 (2d Cir. 2006) (raising the issue of the extent of the express preemption provision regarding medical devices), *cert. granted,* 127 S. Ct. 3000 (June 25, 2007) (No. 06-179); see discussion infra Part VI.

30. See discussion infra Part VI.B.1.


32. See discussion infra Part VI.A–D.

33. See discussion infra Parts VI.E–F.

34. *Id.*
scope. This process would also serve a regulatory interest in resolving the issue with more accountability and would be a more suitable “preemption-worthy federal policy” than the agency’s present approach. 35

Some may object to the suggestions made in this Article for expanding the scope of the disclosures to physicians. These objections include concerns that the information may unduly alarm doctors about uncertain risks and cause a decreased use of drugs that may have important benefits. 36 There may also be concerns about overloading physicians with information. However, the suggestions made here would place the risk signals in a separate part of the physician labeling or the agency’s Safety Information Web Site. Others may believe that more testing, as opposed to more disclosures, is needed to protect the public. While more testing may well be needed in some cases, the aim here is to ensure that, at a minimum, adequate disclosures are made.

The discretionary nature of decisions about drug risks supports the idea of providing better access to information on important pending issues. The IOM found that the “risk-benefit analysis that currently goes into regulatory decisions” varies among review divisions and appears “ad hoc, informal, and qualitative.”37 Other commentators have pointed out that FDA decisionmaking is decentralized and that “policy is largely made at the lowest levels of FDA rather than at the top.”38 An FDA guidance document also described the FDA’s role in making decisions on when to act on emerging risks as “a matter of judgment, about which reasonable people with relevant experience may disagree.”39

Given the judgmental nature of the evaluation, two important issues arise: (1) whether physicians should have access to information on risk signals that can lead to reasonable differences in assessing the seriousness of a potential risk and (2) whether there is a satisfactory way to identify which risk signals are reliable indicators of important potential risks. The underlying issue is whether decisions balancing a drug’s benefits against its emerging risks are best made by the agency, after negotiations with the drug sponsor and sometimes with input from an advisory committee in meetings which may be closed on occasion. 40 This Article suggests


36. See Preemption Statement, supra note 26, at 3,935 (discussing the FDA’s concern about the impact of the current policy in discouraging use of beneficial drugs).

37. IOM REPORT, supra note 4, at 123. The panel recommended use of a “‘value-of-information’ approach” for determining priorities. Id. at 125.

38. HUTT, MERRILL & GROSSMAN, supra note 16, at 19.


40. See 21 U.S.C. § 355(n) (2000) (requiring that the FDA establish panels of experts to provide “expert scientific advice and recommendations . . . regarding a clinical investigation of a drug or the approval for marketing of a drug”); HUTT, MERRILL & GROSSMAN, supra note 16, at 723–24 (providing
that providing physicians with more information about notable risk signals that are under agency review leaves the choice on how to balance a drug’s emerging risks against its benefits not only with the agency but also with the physicians, who can use the information to guide their patients.

To explore this matter, Part II will provide a short history of Vioxx for its relevance in prompting the legislative changes and in providing a concrete setting for identifying the factors that can indicate the need for more disclosures about risks. Part III summarizes the findings of the IOM that bear on this Article, including the reasons why premarket testing of drugs is not adequate to identify the risks that patients may encounter during use. Part III also examines the IOM’s recommendation for a risk management approach to deal with these limits. Part IV notes the most relevant features of the new drug reform legislation, including the provisions on an active surveillance system and the new authority to require postmarket tests and labeling changes.

Part V suggests improvements that should be considered in disclosures about the limits of testing, including the potential for newly-approved drugs in particular to have unknown risks. Part V also describes some key changes that should be considered in the consumer advertising of drugs to ensure adequate risk disclosure. Part VI examines the reasons why the FDA’s preemption policy should be reexamined to promote the accountability of the agency, reinforce the sponsor’s responsibilities, and provide physicians with access to information on important risk signals. Part VII concludes by maintaining that the measures proposed in this Article would help ensure that the safety risks are acknowledged and that the physician has access to information about important risk signals. These improvements promote better consideration of a drug’s risks by the agency and physicians in their decisionmaking. Part VII also concludes by adding some final observations on how the periodic need to renew user fees can affect the relationships between a regulatory agency and the political branches of the government and lead to compromise legislation.

II. OVERVIEW OF THE HISTORY OF VIOXX AND SIMILAR DRUGS

This Part gives a short history of Vioxx in order to identify the lessons it provides on the need for disclosures. Particular attention is given to the risk signals reported in medical reviews and the adequacy of surrogate endpoints to identify risks.

an overview of FDA use of advisory committees and the criteria for nondisclosure of committee materials); see also Tri-Bio Laboratories Inc. v. United States, 856 F.2d 135, 136, 138 (3d Cir. 1987) (upholding, in the context of a new animal drug, the FDA’s position that unpublished safety and effectiveness data on drugs are confidential business information that may not be disclosed until the agency determines that the data are not needed to support approval); FDA Notice, Arthritis Advisory Comm. Meeting, Notice of Meeting, 66 Fed. Reg. 58,745 (Nov. 23, 2001) (announcing that a portion of the meeting would be closed to consider a matter of “some urgency”).
A. Initial Approval

1. Basis

The FDA initially approved Vioxx simply for arthritis pain relief, based on placebo testing. The hope was that Vioxx and the other Cox-2 drugs, such as Celebrex, were “Super Aspirins” that could provide the same relief as other pain relievers being used for arthritis pain but without the serious risk of stomach bleeding from chronic use.

The FDA allowed Merck to make a statement on the drug’s label about “special studies” that showed that treatment with Vioxx, as compared to treatment with ibuprofen, had reduced the number of gastroduodenal ulcers, as shown through a scope test. The FDA did not believe a “surrogate indicator” like this was sufficient to support a claim that Vioxx causes fewer cases of stomach bleeding and required a warning that a long-term clinical outcome study had not been done. A similar statement was permitted for Celebrex, another Cox-2 drug, and the FDA required a similar warning about stomach bleeding.

2. Cardiovascular Risks in the Medical Reviewer’s Report

The possibility that Vioxx was linked to cardiovascular risks was raised in the medical review before Vioxx was first approved. The reviewer gave the following comments:

“The most frequent serious adverse events were of the cardiovascular body system in all study groupings. With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular... events is increased... A

43. PDR, supra note 41, at 1913.
44. Id.
45. Id. at 2902–03.
46. Documents found during litigation, after Vioxx had been withdrawn, indicated that there were reasons, based on biological evidence, that led at least one Merck scientist to believe there was a theoretical risk. See Mathews & Martinez, supra note 3, at A1.
larger database will be needed to answer this and other safety comparison questions.”

When Dr. Sandra Kweder testified for the FDA before the Senate Finance Committee about the decisionmaking process in the approval of Vioxx, she was asked why the labeling did not reflect this potential cardiovascular risk. She accepted the characterization that the information was a “theoretical concern” but not “an evidentiary concern.” The fact that later studies showed a cardiovascular risk led to more attention on the need to disclose risk signals and other issues raised by medical reviewers.

**B. Postapproval Submission for a New Indication**

1. **Benefit Found**

After Vioxx was approved, Merck completed and submitted to the FDA the VIGOR study, which represented the type of testing the agency wanted. The New England Journal of Medicine published an article about the study before it was submitted to the FDA, and its publication undoubtedly made physicians more aware of the drug’s potential benefit and expanded use of the drug as well. The VIGOR study actually confirmed that the drug reduced gastrointestinal bleeding when compared to naproxen, the standard arthritis treatment.

2. **Cardiovascular Risk Findings and the Medical Reviewer’s Report**

The FDA’s medical review of the study found, however, that serious cardiovascular events occurred more frequently among the Vioxx users at the high dose used in the tests—a dose twice the size than that intended for long-term chronic use. In February 2001, the medical reviewer concluded that “there is an
increased risk of cardiovascular thrombotic events, particularly myocardial infarction, in the [Vioxx] group compared with the naproxen group.\textsuperscript{55}

3. Period of Negotiation on the Need for Labeling Disclosures

Merck and the FDA debated for quite some time about whether the result at the higher dose required any change in the labeling, whether the result was due to a protective effect of naproxen, and whether cardiovascular-specific testing was needed.\textsuperscript{56} Finally, the agency and the company agreed on a precaution stating that “[t]he significance of the cardiovascular findings” at the higher dose and in two other studies was “unknown,” that caution was needed by those most at risk, and that prospective studies of the cardiovascular events had not been performed.\textsuperscript{57} The extended time that it took to negotiate the revised labeling in the case of Vioxx influenced legislative proposals to expand the FDA’s statutory powers.\textsuperscript{58}

4. Subsequent Cardiovascular Findings, Voluntary Withdrawal, and Class Effect Assessments

The last part of the Vioxx story relates to another clinical study, known as the APPROVe study. This study was undertaken to determine if Vioxx could help prevent cancer colon polyps.\textsuperscript{59} Merck monitored this study to determine the drug’s cardiovascular effects.\textsuperscript{60} When this study showed statistically significant cardiovascular effects at the low dose, Merck voluntarily removed Vioxx from the market, regarding that study as “[t]he first definitive data” that demonstrated a higher cardiovascular risk,\textsuperscript{61} because it was performed as a “randomized controlled clinical trial” and therefore was “the most persuasive evidence.”\textsuperscript{62}

\textsuperscript{55} Memorandum from Shari L. Targum, FDA Medical Officer, to Sandra Cook, FDA Project Manager, and Maria L. Villalba, FDA Medical Officer, 34 (Feb. 1, 2001), available at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf.

\textsuperscript{56} See \textit{S. Finance Comm. Hearing}, supra note 42, at 59 (statement of Dr. Sandra L. Kweder, Acting Director, Office of New Drugs, Food and Drug Administration) (stating that the labeling change took “a very long time, much longer than usual”); Harris, supra note 2, at A11 (reporting as an explanation for delay that the “F.D.A. does not own a drug’s label, drug makers do. Short of threatening to seize a drug if a label is not changed, the agency must negotiate with drug makers over any change. This can lead to delays”).

\textsuperscript{57} \textit{Physicians’ Desk Reference} 2110 (58th ed. 2004). The revised labeling provided that “caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease” and that further testing had not been done. See \textit{S. Finance Comm. Hearing}, supra note 42, at 42-43 (statement of Dr. Sandra L. Kweder, Acting Director, Office of New Drugs, Food and Drug Administration).

\textsuperscript{58} Harris, supra note 2, at A11.

\textsuperscript{59} \textit{S. Finance Comm. Hearing}, supra note 42, at 62 (statement of Dr. Sandra L. Kweder, Acting Director, Office of New Drugs, Food and Drug Administration).

\textsuperscript{60} \textit{Id.} at 163 (prepared statement of Dr. Sandra L. Kweder).

\textsuperscript{61} \textit{Id.} at 69 (statement of Raymond V. Gilmartin, Charman, President, and CEO, Merck & Co.).

\textsuperscript{62} \textit{Id.} at 88 (prepared statement of Raymond V. Gilmartin).
The FDA responded with a “Public Health Advisory” that recommended limited use of Celebrex and non-steroidal anti-inflammatory drug products (NSAIDS), including naproxen. Later, the FDA found that the data were “best interpreted” as showing “a class effect” for Celebrex, as well as other NSAID painkillers like naproxen, and called for “Black Box” warnings—the strictest warning label—to be added to all these drugs about their potential for cardiovascular effects. By that time, cardiovascular risks had been found in a cancer prevention study of Celebrex, resolving a debate on whether the cardiovascular events should be considered a class effect for this drug.

C. Lessons for Disclosures and the Debate on the Need for Organizational Independence of Safety Decisions

1. Criteria for Warnings

It is notable that Merck had such a demanding test for determining an adequate basis for a warning, withdrawing the drug only when a clinical study found risks at the normal dosage level. Moreover, the FDA’s VIGOR warning, based on an extrapolation from a clinical study using a higher dose, came after a long negotiation.

A test like Merck’s that requires clinical findings before the drug sponsor will implement warnings fails to protect the public adequately because of the inherent limits on detecting risks of drugs in clinical testing. Adequate weight must be given to other evidence, including extrapolations from clinical studies.

2. Weight of Observational Studies and Organizational Changes

At a congressional hearing on Vioxx, an FDA drug safety officer criticized the agency for giving insufficient weight to epidemiological studies and characterized


66. See supra notes 61–62 and accompanying text.

67. See discussion infra Part III.

68. The FDA’s criteria for warnings about a “clinically significant hazard” provide that they should be given “as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.” 21 C.F.R. § 201.57(c)(6) (2007).
the regulatory system as being “broken.” The FDA had placed less weight on the findings from the observational study, considering it less valuable because the study did not identify which patients were taking aspirin or whether the Vioxx patients were already at a higher risk. The testimony also led to proposals for organizational changes that would allow decisions regarding drug safety to be made independently.

III. IOM REPORT ON LIMITS OF TESTING AND RISK MANAGEMENT

This Part focuses on the aspects of the IOM Report that relate to the limits of testing and the way risk information can be identified and evaluated before and after approval. The discussion starts with the scope of the testing currently done to support the approval of drugs and the existing postmarket surveillance techniques. The discussion then turns to the recommendations made by the IOM about postmarket testing and active surveillance of risks. This background illuminates the types of disclosures that should be considered for drugs.

A. Limits of Premarket Testing and Criteria for the Scope of Testing

In a 1999 report, an FDA task force noted that preapproval trials for drugs used on a chronic basis rarely identify long-term effects because “often no more than a few hundred individuals use the product for 6 months or longer.” Despite this problem, “[c]linical trial investigators [still] expect the majority of severe toxicities to be detected through . . . animal studies” and current trials. The protocol designs also “reflect decades-long experience . . . analyzing what can reasonably be achieved during clinical investigations, and carefully considering the practical

69. S. Finance Comm. Hearing, supra note 42, at 13, 15–16 (statement of Dr. David J. Graham, Associate Director for Science, Office of Drug Safety, Food and Drug Administration). Dr. Graham went on to criticize the “world view” present in the office that approves drugs that believes “only randomized clinical trials provide useful and actionable information.” Id. at 16.

70. See Decision Memorandum, supra note 64, at 7.

71. See S. Finance Comm. Hearing, supra note 42, at 163 (prepared statement of Dr. Sandra L. Kweder).

72. See id. at 15 (statement of Dr. David J. Graham, Associate Director for Science, Office of Drug Safety, Food and Drug Administration) (objecting to the view that the Office of Drug Safety should not “reach any conclusions or make any recommendations” without concurrence from the Office for New Drugs).

73. See Phil B. Fontanarosa, Drummond Rennie & Catherine D. DeAngelis, Postmarketing Surveillance—Lack of Vigilance, Lack of Trust, 292 JAMA 2647, 2649 (2004).


75. Id. at 44.
ability of manufacturers and clinical investigators to regularly conduct large-scale trials.  

The recent IOM Report recognizes the limits of preapproval clinical trials and pointed out that “[p]remarket clinical trials are designed primarily with efficacy,” not safety outcomes, in mind.  

The tests may provide little information about long-term exposure because of their short duration and because they “usually do not represent the full array of patients who will use the [drug],” including those who are sick.  

The IOM found that, as a result of the limits, “the safety profile of a [new drug] . . . is especially uncertain” at the time of approval.  

These limitations, though, “are inherent in the system and cannot be changed without adding considerably to the time and expense of drug approvals,” including approvals for beneficial drugs.  

The IOM responds to these limitations by emphasizing the need for improvements in postmarket surveillance and recommending that the FDA have the authority to require additional postmarket trials or observational studies when needed.  

The scope of the testing and surveillance must “match the specific safety concerns and benefits presented by the drug product.”  

The IOM also recommends that the FDA develop a systematic approach and use risk-benefit analysis, rather than continue to use the ad hoc approach that appears to guide its decisions.  

Under these recommendations, the scope of the testing depends on a balance of factors, rather than a bright-line test with a minimum time length and defined parameters, depending on the category of the drug.

B. Difficulties of Postmarket Surveillance and Means of Improvement

Given the limits of preapproval testing, the IOM emphasizes the importance of postmarket surveillance in detecting risks not found in the clinical trials. There also are drawbacks, though, to the existing passive postmarket surveillance system. The present system largely depends upon spontaneous adverse event reports. This approach monitors rare side effects, but not those side effects that are common in the population, such as heart problems.

The IOM recognizes the need for an active postmarket surveillance system, which could transform drug regulation. The first step, aimed at signal generation,
would improve the means of detecting adverse events and increase the use of statistical surveillance systems.\textsuperscript{87} The next step would improve the “formulation and testing” of hypotheses about risks,\textsuperscript{88} including improving access to health care databases to test the hypotheses and implementing “active surveillance” of specific drugs when needed.\textsuperscript{89} If these means do not adequately identify risks, observational or clinical trials may be necessary.\textsuperscript{90}

The development of a systematic approach presents some obstacles, however, because the methods of risk detection are still evolving and data may be missing due to the limits of the preclinical testing and the use of surrogate indicators.\textsuperscript{91} In cases where a risk signal is “apparent but uncertain,” additional studies should be done to “reduce the uncertainty” about the risk.\textsuperscript{92} A “value of the information’ approach” is suggested for determining the priority of further research studies.\textsuperscript{93} The results of any analysis should be made “available to patients, physicians, policy makers, and researchers” to guide their decisions.\textsuperscript{94} The IOM also recommends a risk-management approach to risks, as well as steps to strengthen the agency’s authority, such as the ability to impose fines.\textsuperscript{95}

\textbf{C. Confirmatory Testing}

The IOM suggests that large-scale confirmatory tests are needed regarding important public health matters, even though the cost may be high.\textsuperscript{96} The IOM also recommends a public-private partnership to prioritize the studies and advises that “Congress should capitalize the public share of this partnership.”\textsuperscript{97} Regarding the responsibilities of the drug companies, the IOM recommends that they pay for clinical trials and observational studies needed for drug approval as part of their “specific postmarket study commitments.”\textsuperscript{98}

\begin{itemize}
\item \textsuperscript{87} See id. at 110.
\item \textsuperscript{88} Id. at 114.
\item \textsuperscript{89} Id. at 114–15.
\item \textsuperscript{90} Id. at 169.
\item \textsuperscript{91} Id. at 124–25.
\item \textsuperscript{92} Id. at 125.
\item \textsuperscript{93} Id. This approach prioritizes research studies based on “the expected value of the improvements in outcomes.” Id.
\item \textsuperscript{94} Id. at 126.
\item \textsuperscript{95} Id. at 170. For a discussion of mechanisms that may increase FDA authority, see infra Part IV.B.
\item \textsuperscript{96} See id. at 117.
\item \textsuperscript{97} Id. at 8.
\item \textsuperscript{98} Id. at 118–19. The IOM notes that the FDA does not consider cost-effectiveness. Id. at 126 n.14. The IOM further recommends that the FDA have the authority to adopt risk minimization action plans to reduce risks when other steps fail to do so. Id. at 119–21. These plans typically place limits on the distribution of drugs. The FDA used such a plan to limit the distribution of the acne drug Accutane because of birth defects caused by the drug. Id.
\end{itemize}
IV. LEGISLATIVE CHANGES TO STRENGTHEN FDA AUTHORITY

This Part provides an overview of some important legislative changes that have been enacted in response to the lessons learned from Vioxx, as well as the recommendations in the IOM Report. The new law provides for the development of an active surveillance system to determine adverse drug risks. The FDA can now require risk evaluation and minimization strategies and has express authority to require postmarket tests and safety warnings. The agency can also impose civil money penalties for violations of the law, which will make it a more powerful regulator but only after implementing procedures are established. The new law is complex, though, and it is difficult to decipher exactly how the different provisions work together. At this point, only a general guide can be provided as to its overall impact and applicability.

A. Support for Active Electronic Surveillance of Postmarket Risks: A Technological Fix?

An important change made by the new law, and perhaps its most important change, is the support provided to establish an electronic active surveillance system for postmarket drug risks. In response to the recommendation of the IOM, Congress directed the agency to establish an active surveillance program, 99 a process sometimes referred to informally as “data-mining.” 100 User fees paid by the drug companies will be used to support the new reporting system. 101 The agency is to develop the program using data from federal programs like Medicare and, when available, electronic programs of private health insurance companies. 102 The first step is to develop methods to access and link the data from multiple sources. Congress contemplates that the system will cover records of 100,000,000 patients by 2012. 103 That is about one-third of the country. A system of this magnitude could have implications for wider use of electronic information in health care generally. Appropriately enough, the law calls for compliance with laws that protect the privacy of the patient records. 104

100. IOM REPORT, supra note 4, at 114.
101. § 905(d), 121 Stat. at 949.
103. Sec. 905(a), § 505(k), 121 Stat. at 944 (to be codified at 21 U.S.C. § 355(k)(3)(B)(ii)(II)).
104. Id. at 945 (to be codified at 21 U.S.C. § 355(k)(3)(C)(i)(I)).
If the new surveillance system works as expected, it could provide a “technological fix” to the problems in detecting drug risks, as seen in the experience with Vioxx. The potential for success of this system raises scientific and technical issues beyond the scope of this Article. Furthermore, the agency would seem to need more experience with the system before an adequate assessment can be made of the potential for success. The impact of the system, though, goes beyond simply providing better adverse event reporting. Indeed, under the new law, the agency must consider whether active surveillance would be sufficient to detect adverse events before it can require postmarket studies. Active surveillance is likely to be much less expensive than clinical or other studies, but whether the surveillance methods are as effective is an important issue. Thus, the agency should make periodic public assessments of the strengths and weaknesses of the new surveillance system and the extent to which the system should replace the use of postmarket safety studies. Such a report would receive more attention from scientists and physicians than decisions dealing with particular cases.

B. Risk Evaluation and Mitigation Strategies (REMS) and Postapproval Study and Labeling Requirements

1. REMS Provisions

When a drug is initially approved, drug sponsors can now be required to have a risk evaluation and mitigation strategy (REMS)\textsuperscript{106} regarding postmarket safety when the agency finds that the strategy is needed “to ensure that the benefits of the drug outweigh the risks.”\textsuperscript{107} The agency can require manufacturers of drugs that have already been approved to have a REMS plan if newly available information shows that the strategy is needed to ensure that the drug’s benefits outweigh its risks.\textsuperscript{108} While this new authority helps to implement the risk management recommendations in the IOM Report, this Article focuses on the special standards that apply to requirements for postmarket testing and labeling.

2. New Authority for Postmarket Studies and Labeling and the Need to Determine Procedures

A separate provision gives the agency the specific authority to require postmarket clinical or other studies, an authority the agency did not expressly have when the Vioxx issues arose.\textsuperscript{109} Now the agency can require additional testing after the drug is on the market, but only if the risk relates to “new safety information”\textsuperscript{110}

\textsuperscript{105} Sec. 901(a), § 505, 121 Stat. at 923 (to be codified at 21 U.S.C. § 355(o)(3)(D)).
\textsuperscript{106} Id. at 926 (to be codified at 21 U.S.C. § 355(p)(1)(B)).
\textsuperscript{107} Sec. 901(b), ch. V, 121 Stat. at 926 (to be codified at 21 U.S.C. § 355-1(a)(1)).
\textsuperscript{108} Id. at 927 (to be codified at 21 U.S.C. § 355-1(a)(2)(A)).
\textsuperscript{109} Sec. 901(a), § 505, 121 Stat. at 922–26 (to be codified at 21 U.S.C. § 355(o)-(p)).
\textsuperscript{110} Id. at 923 (to be codified at 21 U.S.C. § 355(o)(3)(C)).
and if the risk is a serious one. The existence of a serious risk can be based not only on information found in clinical trials but also on other tests—presumably including observational studies—as well as adverse event reports that involve death, hospitalization, incapacity, or “other scientific data deemed appropriate” by the agency. However, the agency must find that active postmarket surveillance would not be effective before tests can be required. In addition, the agency must find that other trials would not be sufficient before it can require clinical trials. Despite these prerequisites, this new authority to require postmarket testing has the potential to be a major improvement in the scope of the agency’s ability to require new testing. An important caveat, though, is that the law requires that dispute resolution procedures govern the new authority, but the procedures are not specified in the law. Rather, they are to be determined by the agency by “regulation and guidance.” The implementation, though, may take some time, and it may well be that a new administration, to be elected in 2008 and appointed in 2009, will make the procedural decisions that will enable full use of this substantive authority.

In another important provision that responds to the lessons of Vioxx, the drug sponsor can now specifically be required to make safety labeling changes ranging from boxed warnings to adverse reaction reports. Again, though, the dispute resolution procedures are left to be determined by the agency. Of course, the new procedural requirements should not be implemented or interpreted in a way that would impose procedural hurdles similar to those that existed before the legislative change was made.

C. Strengthened Enforcement Measures

The new law strengthens the agency’s enforcement authority by permitting civil money penalties if a drug sponsor fails to comply with an order pursuant to a dispute resolution proceeding that orders postapproval testing or a safety labeling
change.\textsuperscript{125} These violations can also be remedied by judicial enforcement measures, such as an injunction\textsuperscript{126} or a seizure action,\textsuperscript{127} but the use of this additional express authority allows for appeals through an agency dispute resolution process.\textsuperscript{128} As already noted, the agency must establish the procedures to govern the dispute resolution procedures through agency “regulation and guidance.”\textsuperscript{129}

V. AGENCY IMPLEMENTATION: TESTING STANDARDS, DISCLOSURES, AND CONSUMER ADVERTISEMENTS

The limits of drug testing create the potential that unknown risks may exist, and such risks may be found only through the observation of patients and postmarket testing and surveillance. Given the problems that occurred with the testing of Vioxx, the first step the FDA should consider is the adequacy of the criteria used to evaluate the scope of the clinical testing. This Part begins with a discussion of the adequacy of the testing criteria and the need for disclosures regarding the limits on testing, the use of surrogate endpoints, and specific commitments for postapproval testing and surveillance. This Part also considers the extent to which disclosures on the agency’s new Safety Information Web Site provide a suitable format for disclosures. Additionally, this Part examines the need for disclosures in consumer advertisements about the special risks posed by newly approved drugs. The discussion closes with a survey of FDA authority to require labeling disclosures.

A. Scope of the Testing for Chronic Use Drugs and the Relevant Criteria

A medical expert, who was also a member of the IOM panel that produced the IOM Report, testified in a 2004 Senate hearing that the initial testing for Vioxx, while adequate to determine pain relief, was not “adequate to evaluate side effects,” such as heart attacks, that were common in those that used the drug on a chronic basis.\textsuperscript{130} The same expert later criticized the pending legislation because it did not require sponsors of drugs similar to Vioxx in their level of distribution and duration of use, approved on the basis of a surrogate indicator, to either perform postmarket

\textsuperscript{125} Sec. 902(b)(1), § 303(f), 121 Stat. at 943 (to be codified at 21 U.S.C. § 333(f)(4)). For more background on the procedures and a more complete explanation of the experience with Vioxx, see Gilhooley, supra note 42.


\textsuperscript{127} Id. § 334 (as amended by Pub. L. No. 110-85, § 912(b)(1), 121 Stat. 823, 952 (2007)).

\textsuperscript{128} See. 901(a), § 505, 121 Stat. at 924, 925 (to be codified at 21 U.S.C. §§ 355(o)(3)(F), (o)(4)(F)) (permitting an appeal from an agency determination that either an additional study or clinical trial is needed or a labeling change is required).

\textsuperscript{129} See id. at 924 (to be codified at 21 U.S.C. § 355(o)(3)(F)) (allowing for an appeal using procedures to be established by the agency).

\textsuperscript{130} S. Finance Comm. Hearing, supra note 42, at 18 (statement of Dr. Bruce M. Psaty, Professor, Medicine and Epidemiology, University of Washington). This criticism is similar to the stated drawbacks of standard preapproval trials. See MANAGING THE RISKS, supra note 74, at 43–44.
“large, long-term, randomized clinical trials” to identify the risks or convert the surrogate indicators into “clinically meaningful outcomes.”

As noted earlier, under FDA standards, only a limited number of individuals are usually tested for longer than six months for drugs used on a chronic basis by large numbers of people. One issue raised by the history of Vioxx is whether the testing standards need to be strengthened; this could be accomplished, for example, by increasing the minimum number of subjects to be tested for chronic use drugs. The IOM sets a balancing test for testing procedures that addresses “the specific safety concerns and benefits” of the drug without specifying rigid testing requirements for particular categories of drugs. The IOM also recognizes that the tests could be done before or after marketing.

While the adequacy of testing raises scientific issues, the agency should consider whether it needs to revise its standards for chronic use drugs used by large numbers of people. Further scientific assessment is needed of the adequacy and reliability of the active surveillance system that the agency plans to develop to determine whether the system reduces the need for long-term studies or other types of testing.

B. Disclosures About Limits of Surrogate Endpoints and Chronic Use Testing

If testing for a drug is limited, there should be adequate disclosures. The FDA’s 2006 Physician Labeling Regulations (Physician Labeling Rule) provide that if an indication is based on a surrogate endpoint, the labeling must have “a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits.” The emphasis of this rule is on the limits of the endpoints in determining the efficacy of a drug. While the endpoints may be sufficient to determine efficacy, they may not be sufficient to detect safety problems, particularly those that occur as a result of long-term use. The history of Vioxx provides an illustration of the need for adequate disclosures. If Merck had relied only on the surrogate indicator provided by the scope test and had not undertaken a comparative clinical trial to determine if stomach bleeding was reduced, the cardiovascular risks would not have been uncovered, at least not until after the subsequent long-term cancer prevention study was done.

132. See MANAGING THE RISKS, supra note 74, at 43–44; see also supra Part III.A (discussing the limits of preapproval testing).
133. See IOM REPORT, supra note 4, at 169; see also supra Part III.A (discussing the limits of preapproval testing).
134. See IOM REPORT, supra note 4, at 169.
135. See discussion supra Part IV.A.
137. See discussion supra Part II.A.
In recent years, the FDA has accepted the use of surrogate endpoints in proving the efficacy for drugs without requiring clinical outcome studies.\textsuperscript{138} This policy has expedited the approval of fast-track drugs, such as drugs used to treat AIDS.\textsuperscript{139} Moreover, when user fees were required, there also was an “agreement that, in return for industry paying user fees,” the agency “would commit to improved performance goals” for acting on new drug applications.\textsuperscript{140} The use of surrogate endpoints can help meet these goals, but their ability to detect safety risks is limited.\textsuperscript{141} Because the surrogate indicators do not have the same ability to determine safety risks as clinical trials do, the disclosures in the labeling should indicate these limits and whether long-term follow-up studies are being done. The disclosures can be aimed at indicating the limits of the testing. Another alternative would be for the agency to develop criteria based on evidence-based medicine to make disclosures that rank the strength of the existing support for a drug.\textsuperscript{142}

C. Disclosures on Commitments for Postapproval Tests or Surveillance and Use of the Web Site

1. Commitments as a Condition of Approval

In practice, when drugs are approved, the drug sponsor may make a commitment, at the FDA’s request, to perform a postmarket test. According to the IOM, though, many of these studies are not completed because of a poor study


\textsuperscript{139} See Direct to Consumer Advertising (DTC): Hearing Before the S. Subcomm. on Consumer Affairs, Foreign Commerce and Tourism, S. Comm. on Commerce, Science, and Transportation, 107th Cong. 6 (2001) [hereinafter DTC Hearing] (statement of Nancy Ostrove, Deputy Director, Division of Drug Marketing, Advertising, and Communications, Food and Drug Administration) (stating that DTC reminder advertisements do “not need to include risk information”).


\textsuperscript{141} See IOM REPORT, supra note 4, at 124–25 (recognizing the potential limits that surrogate endpoint testing may have).

design, the difficulties of enrolling patients,\textsuperscript{143} the lack of FDA power to compel completion,\textsuperscript{144} “high costs,” and the fear of “unfavorable results.”\textsuperscript{145} The status of the studies is already disclosed in the Federal Register but should now also appear on the new Safety Information Web Site.\textsuperscript{146} If the failure to complete the study significantly affects the assessment of the safety of the drug, the sponsor and the agency should provide an appropriate disclosure in the physician labeling as well. These steps are necessary because patients will still be using the drug while this postapproval testing and surveillance is being done, and these studies may be the principal means of discovering risks of chronic use drugs with limited preapproval testing. Strengthening the FDA’s enforcement powers may lead to increased compliance with these commitments to do postmarket testing.

2. Commitments After Approval

Risks for which the FDA requests the drug sponsor do additional clinical or observational studies or other types of monitoring should be disclosed, at least on the agency’s web site, when such risks are identified after the drug has been placed on the market. Disclosing that the FDA has required these follow-up measures indicates that the agency believes there is a potential risk that cannot be ignored. Requests for more studies or monitoring also defers resolving the need for a warning.\textsuperscript{147}

Under the new law, there will be new forms of active surveillance that may identify issues that present close and novel questions as to whether a warning is needed or whether further investigation is sufficient.\textsuperscript{148} Indeed, there could be a spectrum of successive follow-up efforts and observational studies that never result in a warning because the evidence is not considered sufficiently definitive. Disclosing the pendency of follow-up measures will at least identify the risk as one worth watching while more research is done to determine if the risk is serious enough to require a warning.

\textsuperscript{143} See IOM REPORT, supra note 4, at 49–50 (pointing out that commitments made by drug companies when a drug is initially approved may not be fulfilled because the commitments are often sought late in the process and may prove “infeasible or unjustified for a variety of reasons” including difficulty in recruiting patients).

\textsuperscript{144} Id. at 115.

\textsuperscript{145} Id. at 116.

\textsuperscript{146} See 21 U.S.C. 356b(c)–(d) (2000 & Supp. II 2002) (providing for reports in the Federal Register and on the agency’s Internet site); see also supra text accompanying note 18 (discussing establishment of a new Safety Information Web Site).

\textsuperscript{147} Indeed, the Vioxx situation involved an undertaking by the drug company to continue to monitor an ongoing study; this monitoring revealed a cardiovascular risk. See discussion supra Part II.B.4.

\textsuperscript{148} See discussion supra Part IV.A.
D. Format for Active Surveillance Reporting

1. Present Reporting of Adverse Events: Passive Surveillance

Under the FDA’s present regulations on postmarketing requirements, there is a separate section for “adverse reactions” that are “reasonably associated with use of a drug.” Adverse reactions must be disclosed, even if causation has not been “definitely established.” The reports are to be presented in a tabular form that permits an overview of their relevance and seriousness.

2. Observational Studies, Active Surveillance, and the Role of the Web Site for Disclosures

Unfortunately, no provision is made in the present labeling requirements for the reporting of risks found in epidemiological or observational studies. While these studies are more limited in their ability to determine causation as compared to the abilities of clinical trials, they appear to be more reliable and significant than passive adverse event reports.

The new law does, however, require the agency to establish a new web site on postmarket safety information (Safety Information Web Site) to provide better access for patients and providers. Furthermore, summaries of the active surveillance data on known serious side effects and unusual increases in risks or new types of risks must appear on the web site. This web site is an important development in making this information accessible to the general public.

The development of the Safety Information Web Site raises the issue of whether the suggested disclosures regarding the pendency of specific postmarket studies and potential risk signals should be made on the web site or whether the disclosures should be contained in the physician labeling. Placing notices in the labeling better ensures ready access of information to the physician, but overload of information would be a concern. In this electronic age, the web site could be a useful means for providing disclosure on less essential matters without the risk of overload on the official labeling. For the web site to be an adequate source for relevant information, though, the printed version of the sponsor’s official labeling should reference the availability of more information on risk signals on the FDA’s web site, and the electronic version of the official labeling should provide a link to the agency web site and its section on risk signals.

149. 21 C.F.R. § 201.57(c)(7) (2007).
150. See id. § 201.57(c)(6).
153. See 915, § 505, 121 Stat. at 958 (to be codified at 21 U.S.C. § 355(r)(2)(D)); see discussion supra Part IV.A.
E. Disclosures About Risks Found in Medical Reviews

1. Risk Signals Found in Medical Reviews Based on Clinical Studies to Support Approval

The labeling or web site should identify the risk signals found by medical reviewers based on clinical studies done at the time of approval or submitted to the FDA to support a new use for a marketed drug. The risks found in Vioxx demonstrate the need for such measures.\(^{154}\) The medical review done when the drug was initially approved noted the frequency of cardiovascular findings in various studies and the need for a larger database to answer whether the risk was increased. The postmarket VIGOR study for Vioxx was intended to demonstrate an added benefit of the drug, but, according to the FDA’s medical review, there was an increase in cardiovascular effects at a high dose in the clinical tests compared to an existing drug.\(^{155}\) When a drug is already on the market, there is a special need for disclosure, even if the FDA and the drug’s sponsor are still negotiating whether a warning or other action is needed.

This proposal would require disclosure of the factual and scientific findings made in a medical review of a clinical test submitted to obtain initial approval or to support a new approved use after the drug is on the market. The disclosure would be listed as a risk signal if the FDA does not dispute the finding when the drug is approved.\(^{156}\) In the case of a review of a study to support a new use for a marketed drug, as occurred with the VIGOR study for Vioxx, any disclosure would be delayed for two months after the completion of the medical review to permit the agency to consider whether the factual findings need to be corrected. The time for including the report in the labeling could be extended for an additional two months but only if authorized in writing by the Commissioner of the FDA. Requiring action by the Commissioner would provide greater assurance that there is a legitimate need for delay and that there is a commitment by the agency to a timely resolution. The disclosure should be listed under a heading for Risk Signals in the new postmarket Safety Information Web Site\(^{157}\) that the agency will be establishing, if it is not included in the physician labeling. If the agency disagrees with the finding, the agency’s disagreement should be described.\(^{158}\)

\(^{154}\) See discussion supra Part II.B.2.

\(^{155}\) See id. When the assessment in the review is based on a meta-analysis, the finding would be included in the risk signal section, unless the agency disagrees with the finding in which case a summary of the disagreement would be given as discussed in the following section.

\(^{156}\) On the other hand, if the FDA disagrees with the assessment, the finding in the review and the reason for the disagreement would be listed in the summary described below.

\(^{157}\) See 915, § 505, 121 Stat. at 957 (to be codified at 21 U.S.C. § 355(r)(2)). The agency can include “other material determined appropriate” on the web site. Id. at 958 (to be codified at 21 U.S.C. § 355(r)(2)(B)(viii)).

\(^{158}\) In case of disagreements, an alternative would be to include the medical review findings and the agency’s position with the summaries in the web site rather than in a section on risk signals.
2. Summaries of Medical Reviews for Approved Drugs and Postmarket Safety Reviews

Under the new law, summaries of “critical issues” for drugs identified in medical reviews at the time of approval by all disciplines will be made available on the agency web site after the drug is approved. No changes can be made in the review by supervisors but disagreements can be noted. Because the summaries are to include issues identified by all disciplines, issues raised by drug safety officers will also be noted. These provisions help to address the concerns raised in hearings before Congress that the FDA does not give enough weight to the findings of the office concerned with drug safety when the drug is approved.

The availability of medical review findings has been particularly controversial in the case of postapproval safety reviews and observational studies. The agency has generally maintained that medical reviews are “predecisional” and that they may contain errors that, if disclosed, might lead fewer people to use a beneficial drug. In the agency’s view, the staff assessments of the studies should be released only “on a case-by-case basis.” The wider range of the issues about disclosure of medical reviews is beyond the scope of this Article, though, and the recommendation discussed above looks at disclosures about medical reviews of clinical studies at the time a drug is approved or a new use is sought.

F. Risk Potential of Newly Approved Drugs and Consumer Advertising

1. IOM Recommendation

Given the limits of testing and postmarket surveillance, the IOM makes the notable recommendation that the agency conduct a comprehensive review of the data on a drug’s safety and efficacy no later than five years after the approval of a “new molecular entity.” The IOM also recommends that the label and promotion to physicians contain a symbol or designation for newly approved drugs

159. 916(3), § 505(l), 121 Stat. at 959 (to be codified at 21 U.S.C. § 355(l)(2)(C)(iv)).
160. Id. (to be codified at 21 U.S.C. § 355(l)(2)(A)(i)).
161. Id. (to be codified at 21 U.S.C. § 355(l)(2)(D)).
162. Id. (to be codified at 21 U.S.C. § 355(l)(2)(C)(iv)).
163. Id.
165. See Gardiner Harris, Potentially Incompatible Goals at the F.D.A., N.Y. TIMES, June 11, 2007, at A14 (reporting that officials responsible for drug-safety were “punished or ignored” after recommending a boxed warning for the diabetes drug Avandia and now advocate a timeline of one to two months for an agency response to safety questions); see also Gardiner Harris, F.D.A. Remains Unsettled in Wake of New Questions, N.Y. TIMES, May 31, 2007 at A14 (reporting tensions between those who approve drugs and those who track postapproval safety).
166. FDA’S RESPONSE, supra note 102, at 14.
167. Id. Furthermore, the agency will make only the final agency review available. Id.
168. See IOM REPORT, supra note 4, at 12.
to indicate that the full risks of the drugs are not presently known.\textsuperscript{169} The IOM further advises a moratorium on advertising of prescription drugs to consumers in the initial years of sale so that physicians may gain information about a drug’s risks as that information becomes available.\textsuperscript{170}

2. Mixed Congressional Response on Consumer Advertisements for Newly Approved Drugs

The new law provides for a periodic reassessment of newly approved drugs in the years after approval.\textsuperscript{171} While not designated as a comprehensive review, the reassessment may serve a similar role. Unfortunately, Congress did not adopt the moratorium on consumer advertising recommended by the IOM because it was concerned that the measure would not meet the heightened constitutional protection provided for commercial speech.\textsuperscript{172} This concern illustrates the powerful influence such constitutional protections have on FDA-regulated products.\textsuperscript{173}

In the absence of a moratorium, the IOM suggests that any consumer drug advertisement discloses that the data related to the new drug’s risks and benefits “are less extensive than those related to alternative products that have been in use for a longer period.”\textsuperscript{174} The IOM suggests the use of a symbol to convey this message after a study had been done on the most appropriate symbol to be used.\textsuperscript{175} The new law does not provide for such a disclosure and instead only provides for a report to Congress on the use of a symbol to designate newly approved drugs in the labeling and in consumer advertisements.\textsuperscript{176} While a symbol may be enough in the physician labeling, a textual statement would certainly be more helpful to consumers, and the agency should recommend that advertisements for newly-approved drugs contain a disclosure that the risks from such drugs are not fully known.

\textsuperscript{169} Id. at 11–12.
\textsuperscript{170} Id. at 11.
\textsuperscript{172} See 153 CONG. REC. S5764 (daily ed. May 9, 2007) (statement of Sen. Kennedy) (stating that senators had concerns about the constitutionality of a moratorium, even when limited to extraordinary circumstances and had therefore reached a compromise that did not impose a moratorium but instead provided for “strong safety disclosure”).
\textsuperscript{173} See Thompson v. W. States Med. Ctr., 535 U.S. 357, 377 (2002) (holding that the prohibition on advertising and soliciting prescriptions for compound drugs in the Food and Drug Administration Modernization Act of 1997 to be an unconstitutional constraint on commercial speech); see also IOM REPORT, supra note 4, at 159–62 (discussing cases in which FDA attempts to regulate consumer advertising have been challenged as unconstitutional). However, the Court’s decision in \textit{Western States} is of little relevance because the drugs there did not pose the same safety risks; the drugs were not widely used; and their risks were discoverable without postmarket surveillance. See Margaret Gilhooley, \textit{Drug Regulation and the Constitution After Western States}, 37 U. RICH. L. REV. 901, 917–21 (2003) (discussing the FDA’s policy for regulating consumer advertising after \textit{Western States}).
\textsuperscript{174} IOM REPORT, supra note 4, at 171.
\textsuperscript{175} Id. at 171–72.
\textsuperscript{176} § 904, 121 Stat. at 944.
3. Prereview of Direct-to-Consumer (DTC) Advertisements

Congress did take an important step to reduce the risk of deception from DTC advertisements by authorizing a prereview of television advertisements. The agency can require changes in the advertisements if it determines that specific disclosures are needed to prevent the advertisement from being “false or misleading.” After a formal hearing, the agency may impose civil monetary penalties of up to $250,000 for broadcasting an advertisement that is false or misleading. Any party who wishes to dispute the decision may seek judicial review. The requirement for a prereview may still face constitutional challenges, but it may be permissible because regulation of false or misleading commercial speech is acceptable.

4. Elimination of Consumer Reminder Advertisements

Under the FDA’s guidance for DTC ads, drug manufacturers should identify important risk information in the ads. However, the risk information need not be provided if the DTC ad is a “reminder” ad, which is an ad that gives the product’s name but not its use. Reminder ads permit sponsors of a drug like Vioxx to run DTC ads without making the same disclosures about risks ordinarily needed in advertisements broadcast to consumers. Reminder ads may be appropriate for doctors who have ready access to drug labeling and are more familiar with the drugs, but consumer advertisements should disclose the risks the drugs pose and not provide only a partial message.

177. Sec. 901(d)(2), § 503, 121 Stat. at 940 (to be codified at 21 U.S.C. § 353(b)(e)(2)).
178. Sec. 901(d)(4), § 303, 121 Stat. at 940–41 (to be codified at 21 U.S.C. § 333(g)(1), (2)).
179. Id. at 941 (to be codified at 21 U.S.C. § 333(g)(6)).
182. See supra note 139.
183. Reminder ads are permitted by regulation in promotion to physicians. 21 C.F.R. §§ 201.100(f), 202.1(e)(2)(i), 801.109(d) (2007). The new law allows the regulations on drug advertisements to be issued through a less formal rulemaking process than had previously been required. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, sec. 901(d)(6), § 502(n), 121 Stat. 823, 941 (to be codified at 21 U.S.C. § 352(n)).
184. The agency should also reexamine the need for patient labeling for advertised drugs given Americans’ lack of awareness of patient labeling and the IOM’s recommendation to establish an advisory committee to improve communication with the public. IOM REPORT, supra note 4, at 185, 188–89.
G. Authority for Labeling Disclosures

If the FDA were to require more disclosures about the risk signals, there may be an issue as to the source of the agency’s authority to require such disclosures. This section surveys the agency’s authority to require labeling authority and its relationship to these disclosures. The law requires drug sponsors to provide “adequate warnings against . . . unsafe dosage or . . . duration of administration” that are necessary for the protection of users. The FDA can also require the labeling to contain both information whose absence would make the labeling misleading by failing to reveal material information and information about material consequences of use. These provisions justify providing information to physicians about the potential for significant risks, which could affect their assessments of whether the drug is safe. Moreover, the safety of the drug is not fully established in the testing done to support drug approval, even though the sponsor has a continuing burden to show that the drug is safe. Physicians should have the benefit of any good indicators of potential risks that are available to supplement their understanding of the safety of the drug. Finally, the disclosures better equip the physician to obtain the patients’ informed consent to the drug’s use. Drug labeling has long provided information about adverse events as a way to inform doctors about risks posed by drugs that are only discovered postmarket. The agency derives its authority to require drug labeling from its authority to require the sponsor to establish records and report data, obtained through clinical experience or otherwise, that are relevant to assess the propriety of continued marketing. The risk signal information suggested here serves as an extension of the adverse event reporting by highlighting notable risks that physicians should watch for in assessing patients’ responses to a drug. Providing information about these risk signals to physicians would also address the loss of public confidence in the safety of drugs that are discovered to have risks known to the FDA and drug sponsor but not disclosed to physicians.

185. 21 U.S.C. § 321(n) (2000); see also Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166, 178 (D.D.C. 2000) (deferring to the FDA’s determination as to whether the definition of “materiality” includes consumer interest, consumer safety, or both).

186. § 321(n).

187. 21 U.S.C. § 352(a); see also Pharm. Mfrs. Ass’n v. FDA, 484 F. Supp. 1179, 1183–86 (D. Del. 1980), aff’d per curiam, 634 F.2d 106, 108 (3d Cir. 1980) (upholding requirements for providing certain drug risk information to patients because the warnings were material with respect to consequences of use).

188. See § 355(d)(4) (providing that a drug can be disapproved based on the application or other evidence if there is “insufficient information to determine whether [the] drug is safe”); see also § 355(e)(2) (providing that a marketed drug can be withdrawn if the evidence available in the application or new evidence “shows that [the] drug is not shown to be safe”).

189. See 21 C.F.R. § 201.57(c)(7) (2007) (discussing the scope of required warnings about possible adverse reactions).


191. See Bright, supra note 2.
Of course, if the present law does not provide adequate authorization to require disclosures of risk signals such as these, a legislative change should be considered. There may be constitutional limits, though, on the ability of a legislature to require labeling if the disclosure is made merely to satisfy the consumers “right to know” or public curiosity. The disclosures proposed here serve to prevent deception and should not be subject to such a restriction on Congress’s ability to require labeling.

VI. FDA PREEMPTION POLICY: DRAWBACKS AND ALTERNATIVES

Highly contentious issues arise in deciding whether a warning concerning new risk information needs to be added to the labeling of marketed drugs and, in turn, whether the agency must agree to the change in advance. The answer affects the scope of liability of drug companies, which can be enormous. This Part begins with an overview of the FDA’s existing rules on providing warnings and the provision in the new law that refers to authorized changes without prior approval. This Part goes on to describe the agency’s position given in its 2006 Preemption Statement. A number of cases are pending that test the agency’s position, and the Supreme Court has invited the Solicitor General to file a brief expressing the views of the United States on a petition for certiorari in a case in which the underlying issue is whether FDA regulation is minimal. This Article, however, does not address the legal aspects of preemption directly.

This Part also considers the merits of the FDA’s Preemption Statement with respect to ensuring the accountability of the agency, reinforcing the drug sponsor’s responsibility to take initiative to reduce risks, and providing access to factually-supported risk information. This Part suggests that the agency reconsider and withdraw its present Preemption Statement. Then, this Part proposes that the agency provide for Disclosure Determination Petitions from the drug sponsor if there is uncertainty about the need for a warning. The petitions would be disclosed as under review after a limited assessment period in a process similar to the proposal regarding potential risk signals discussed above. This Part finally addresses the merits of this approach as compared to the approach detailed in the agency’s

192. Int’l Dairy Foods Ass’n v. Amestoy, 92 F.3d 67, 73 (2d Cir. 1996) (finding that the consumer’s “right to know” is not a substantial governmental interest that justifies a restriction on commercial speech (quoting Int’l Dairy Foods v. Amestoy, 898 F. Supp. 246, 249 (D. Vt. 1995)) (internal quotation marks omitted)).


194. Levine, 127 S. Ct. 2451 (2007); see also cases cited supra note 29 (discussing issues pending before the Supreme Court on the preemptive effect of FDA regulations).

195. See discussion supra Part V.E.1.
Preemption Statement, and then concludes by discussing the issues these approaches raise.

A. FDA Regulation of Criteria for Warnings and Changes Without Prior Approval

Drug sponsors are required to report serious adverse events to the FDA within fifteen days of the event’s occurrence.\footnote{196} The FDA’s regulations for warnings about risks in physician labeling provide as follows: “In accordance with [section] 314.70 . . . , the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; [however,] a causal relationship need not have been definitively established.”\footnote{197}

Section 314.70 generally requires manufacturers to obtain the agency’s advance approval for changes in the drug’s labeling.\footnote{198} However, the rule also permits Changes Being Effected (CBEs) immediately that are made to “add or strengthen . . . a warning” to be added to the label simply by providing notice to the agency.\footnote{199} The effect of this provision is to allow for possible products liability claims for a failure to warn of risks that the FDA has not required or approved.\footnote{200}

B. FDA Preemption Statement and Regulatory Change in the Final Rule

1. Need for Preemption

In the preamble to a rule that revised the format and content of physician labeling, the FDA endorsed a broad view of the need for preemption of products liability. This Preemption Statement is based on the authoritative regulator model and emphasizes the agency’s “statutorily prescribed role as the expert [f]ederal agency responsible for evaluating and regulating drugs.”\footnote{201} According to the agency, state tort actions can “encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug” and create “pressure on manufacturers to attempt to add warnings . . . [and] to propose ‘defensive labeling’ . . . , which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.”\footnote{202} The

\footnote{196} 21 C.F.R. § 312.32(d)(3) (2007). The information reviewed by the drug sponsor in making a report may come from scientific literature, postmarketing studies, or any source obtained by the drug sponsor. \textit{Id.} §§ 312.32(b), (d), (e).
\footnote{197} § 201.57(c)(6)(i).
\footnote{198} § 314.70(a).
\footnote{200} See Osburn v. Anchor Labs., Inc., 825 F.2d 908, 911–14 (5th Cir. 1987).
\footnote{201} Preemption Statement, \textit{supra} note 26, at 3,935.
\footnote{202} \textit{Id.}
agency further maintains that state tort actions encourage a “misunderstanding” that “FDA labeling requirements represent a minimum safety standard,” even though the FDA interprets the law as creating “both a ‘floor’ and a ‘ceiling’ . . . [for imposition of liability] if the additional statement[s] are unsubstantiated or . . . misleading.”

The FDA also identified the limited role it saw for CBEs, explaining that whether labeling revisions are necessary is, in the end, squarely and solely FDA’s [determination] under the act. A manufacturer may, under FDA regulations, strengthen a labeling warning, but in practice manufacturers typically consult with FDA before doing so to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to enforcement action).

As a result the agency found that “at least” a number of claims would be preempted by the CBE provision, including tort suits based on a failure to provide a “statement” in the labeling, “the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA.”

2. Procedural Issues and Puzzling Regulatory Change in 21 C.F.R. § 314.70

The agency also made a puzzling change in the final rule that seems to minimize the use of the CBE process for substantive warnings and to have done so in a way that raises procedural issues. In a convoluted revision in the procedures for making changes, the FDA has precluded any changes in the Highlights section that are made by the CBE procedure other than editorial changes such as removal of a provision from the “[r]ecent major changes” section. The preamble to the Preemption Statement explains that, because of the importance of the Highlights section, the agency revised Section 314.70 to require sponsors “to obtain prior approval of any labeling changes to Highlights, except for editorial or similar minor changes.” The Physician Labeling Rule, though, expressly states that the new Highlights section in the labeling shall include “[r]ecent major changes” to the “full prescribing information” in the labeling, including warnings “that contain[] substantive labeling changes that have been approved by the FDA or authorized

203. Id. at 3,934–35.
204. Id. at 3,934.
205. Id. at 3,935–36.
206. See 21 C.F.R. § 314.70(c)(6)(iii) (providing that changes in the Highlights section in 21 C.F.R. § 201.57(a) must be made pursuant to section 314.70(b)(2), which requires prior approval of the agency, except for changes made under section 314.70(b)(2)(v)(c), which are changes that either remove a listing or change a date).
207. See Preemption Statement, supra note 26, at 3,932.
under [Section] 314.70(c)(6),” the very provision that authorizes CBE changes without the FDA’s prior approval.208

If this change in the final rule is intended to limit the type of changes that can be made by the CBE procedure to those that are merely editorial, it would seem to be not only inconsistent with the text but also to be a significant change. Such a change would warrant a reproposal of this aspect of the rule to provide notice and an opportunity for public comment.209 This is especially so because the proposed rule raised concerns about products liability only with respect to whether the proposed Highlights section could increase liability rather than with the need for limits generally.210

C. State of Litigation on Preemption

The courts are split on whether the assertion of preemption is consistent with FDA regulations and whether an FDA assertion of preemption is entitled to deference.211 A district court found the FDA’s preemption position inconsistent with the affirmative obligation of a drug manufacturer under the CBE regulation to add warnings as soon as there is evidence of a reasonable association between use of a

208. 21 C.F.R. § 201.57(a)(5) (2007). Subsection (a)(10) of this rule provides for a “summary of the most clinically significant” warnings. Id. § 201.57(a)(10). The full prescribing information about the warnings is given later in the labeling as provided for in subsection (c)(6). Id. § 201.57(c)(6).

209. See 5 U.S.C. § 553(c) (2000); Natural Res. Def. Council v. Envtl. Prot. Agency, 279 F.3d 1180, 1188 (9th Cir. 2002) (holding the EPA needed to make another proposal when the changes represented “a fundamental policy shift”). While general statements of policy can be issued without the use of notice-and-comment rulemaking, the statement must not be binding, a matter not considered here. See § 553(b)(A) (2000).

210. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels. 65 Fed. Reg. 81,082, 81,086 (Dec. 22, 2000). The statement of the potential impact of the proposed rule on federalism also stated that the proposal “does not preempt State law.” Id. at 81,103.


drug and adverse side effects. The FDA’s position has also elicited both support and objections and reservations in legal commentary. Earlier articles have examined the appropriate place for regulatory compliance in dealing with postapproval risks.

The Supreme Court is considering granting certiorari in Levine v. Wyeth, where the Vermont Supreme Court found that tort liability did not conflict with federal law or goals, FDA regulation was minimal regulation, and the FDA Preemption Statement was unpersuasive and did not warrant deference. The Court has also agreed to examine the FDA’s express preemption provision for

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214. See William Funk et al., The Truth about Torts: Using Agency Preemption to Undercut Consumer Health and Safety, CENTER FOR PROGRESSIVE REFORM WHITE PAPER, September 2007, at 1, 2, available at http://www.progressiveregulation.org/articles/Truth_Torts_704.pdf (arguing that federal preemption of common law tort cases would damage the rights of consumers and patients to recover damages); David A. Kessler & David C. Vladeck, A Critical Examination of the FDA’s Efforts to Preempt Failure-to-Warn Claims, 96 GEO. L.J. (forthcoming 2008), available at http://lsr.nellco.org/georgetown/ois/papers/2/ (commenting on the FDA’s efforts to convince courts that failure-to-warn cases are preempted by federal regulation); Nagareda, supra note 35, at 4–5 (urging the use of the availability of preemption as an instrument to bolster the predicates for preemption with the FDA process); O’Steen & O’Steen, supra note 199, at 69 ("[P]olicy considerations favor abandoning the doctrine of preemption as applied to drugs and medical devices regulated and approved by the FDA."); Catherine M. Sharkey, Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State Versus Federal Courts, 15 J.L. & POL’Y 1013, 1017–21 (2007) (noting a decline of the regulatory compliance defense and the critical role of federal agencies which may make them the “driving force” behind the federal-state disparity in preemption determinations); Catherine M. Sharkey, Preemption by Preamble: Federal Agencies and the Federalization of Tort Law, 56 DEPAUL L. REV. 227, 228, 258–59 (2007) (examining the “momentum towards” increased use of preemption by federal agencies and the corresponding court deference to agency determinations).

215. See Michael D. Green, Statutory Compliance and Tort Liability: Examining the Strongest Case, 30 U. MICH. J.L. REFORM 461, 496–97 (1997) (noting the reasons why postmarket surveillance should be required); Robert L. Rabin, Reassessing Regulatory Compliance, 88 GEO. L.J. 2049, 2079, 2084 (2000) (finding that the defense of regulatory compliance has “virtually no relevance” for risks found postmarket and may need to be “case-specific”); Richard B. Stewart, Regulatory Compliance Preclusion of Tort Liability: Limiting the Dual Track System, 88 GEO. L.J. 2167, 2167, 2186 (2000) (maintaining that an ALI proposal on regulatory compliance is “sound and should be implemented” but pointing out that the proposal only provides for compliance preclusion for those risks that “specifically have been addressed and regulated by the administrative program”).


217. Id. at ¶¶ 32–34. The Court has asked for the Solicitor General’s views on the petition for certiorari. Levine, 127 S. Ct. 2451; see discussion infra Part VLE for further discussion of this case and the relevance of the Preemption Statement.
medical devices and how it applies to tort liability. While there is no similar provision governing drugs, there is always the prospect that the Court’s decisions in these cases may have broader implications.

D. Relevance of the Legislative Provision that New Authority Is Not to “Affect” the CBE Rule

The new law gives the agency express authority to request labeling changes to reflect new safety information and to order such changes after a dispute resolution process. Fines can be imposed for violations and failure to obey the order can lead to the imposition of civil monetary penalties. The law provides that this new authority “shall not be construed to affect the responsibility of the [sponsor] . . . to maintain its label in accordance with existing requirements,” including 21 C.F.R. § 314.70, the provision that permits CBE changes without prior agency review. According to a newspaper report, a rule of construction was sought by House Democrats and plaintiff lawyers who believed the reference to the responsibility of manufacturers to “maintain” their labels would weaken preemption as a shield against products liability.

E. Policy Reasons for Reconsidering the Preemption Statement

The aim of this section is to examine the preemption debate and the alternative approaches from a policy perspective. The discussion suggests that, even without regard to any legal difficulties encountered with the Preemption Statement, the FDA should withdraw the statement and develop a new approach because of the statement’s policy-related drawbacks. These drawbacks relate to the limited accountability for agency inaction, the lack of an incentive for drug sponsors to consider making various necessary changes, and the lack of public information about the basis for the sponsor’s and the agency’s positions. These drawbacks are illustrated by looking at the impact of preemption under the agency’s policy like

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218. See Riegel v. Medtronic, Inc., 451 F.3d 104, 106 (2d Cir. 2006), cert. granted, 127 S. Ct. 3000 (June 25, 2007) (No. 06-179); see also Linda Greenhouse, Supreme Court Hears Medical Device Case, N.Y. TIMES, Dec. 5, 2005 at C3 (reporting concern voiced by some Justices during the oral argument about shielding manufacturers before the FDA had learned of a risk or took action).


220. Sec. 902(b)(1), § 303(f), 121 Stat. 823, 943 (to be codified at 21 U.S.C. § 333(f)(4)).

221. Sec. 901(a), § 505, 121 Stat. at 925–26 (to be codified at 21 U.S.C. § 355(o)(4)(I)).

222. See supra note 199 and accompanying text.

that presented by Vioxx. The Levine case\textsuperscript{224} is also instructive on the policy issues whether or not the Supreme Court reviews the case.

1. Accountability of the FDA

The first reason the FDA should consider developing a new preemption policy is that the agency does not have to make a decision or publicly disclose the situations in which its policy will prevail. Preemption can involve inaction by the agency if “the substance” of the warning sought in the liability suit had been “proposed to FDA for inclusion in labeling” by the drug sponsor but “that statement was not required by FDA.”\textsuperscript{225} Indeed, it seems that preemption might even occur when the sponsor opposes the agency’s efforts to obtain a warning, such as when there were long negotiations over the warnings needed for Vioxx.\textsuperscript{226} The scope of the coverage presents other questions as well. For example, would a routine change to the list of adverse events be sufficient to count as the “substance” of a warning about a risk and one that had been “proposed”?\textsuperscript{227} Is the substance of a statement proposed if it is only oral, and will there be any record of the specific warning the sponsor sought? Would the length of the negotiations between the sponsor and the agency be relevant? If the agency is to be accountable, it needs to make a decision as to whether any warning or disclosure is needed or, at a minimum, make public that it is still deciding the issue. The current policy expressed in the Preemption Statement fails to provide this level of accountability.\textsuperscript{228}

2. Reinforcing the Sponsor’s Responsibility

The FDA’s preemption policy erodes the incentive provided by the threat of liability that holds drug sponsors responsible for examining the necessary steps that should be taken to reduce risks associated with the use of their drug. Under the FDA’s preemption policy, the sponsor’s responsibility is determined by the FDA’s decision to press for a change that exceeds what the sponsor may have proposed, rather than by what a reasonable sponsor would propose to reduce a drug’s risk. The sponsor should have to identify why a more stringent warning, including a boxed warning, is not needed.

\textsuperscript{224} 2006 WL 3041078, at ¶ 23 (finding more warnings needed about the risk of amputation from inadvertent insertion of a push injection into an artery, and regarding an alternative raised by the sponsor and not accepted by the FDA as “different, but not stronger”).

\textsuperscript{225} See Preemption Statement, supra note 26, at 3,936; see also discussion supra Part VI.B.1.

\textsuperscript{226} See discussion supra Part II.B.3.

\textsuperscript{227} 153 CONG. REC. S5764 (daily ed. May 9, 2007) (statement of Sen. Kennedy).

\textsuperscript{228} See Heckler v. Chaney, 470 U.S. 821, 837–38 (1985) (holding that an agency’s decision not to institute proceedings is not actionable “unless Congress has indicated otherwise”).
3. Physician Access to Information

The Preemption Statement does nothing on its own to provide physicians with access to important new risk concerns, such as the cardiovascular risks associated with the use of Vioxx found in the VIGOR study.\textsuperscript{229} Of course, the new law strengthens the agency’s enforcement authority, which should facilitate its ability to obtain information and make it easier to take enforcement action against drug sponsors that fail to provide physicians with adequate warnings.\textsuperscript{230} However, the implementation of the expanded authority depends upon the issuance of new regulations and guidance.\textsuperscript{231} As a result, ensuring that there are adequate disclosures about pending issues continues to be important.


Under its preemption statement, the FDA encourages drug sponsors to consult with the agency about the need for labeling changes.\textsuperscript{232} As illustrated by Levine,\textsuperscript{233} these consultations may involve letters from the drug sponsor about a proposed change that involve subtle differences in the wording that can lead to different assessments about whether they represent a strengthened warning.\textsuperscript{234} The drug sponsor maintained that the FDA’s decision to retain the original warning preempted a tort claim that a stronger warning was needed.\textsuperscript{235} The dissent maintained that the sponsor’s proposal gave the opportunity to the FDA to consider the adequacy of the warning in general.\textsuperscript{236}

The sponsor’s proposal, though, was not well adapted to that broader aim. There is no clear indication, for example, about what level of increased risk had prompted the drug company to believe a change was needed or whether the sponsor raised the need for a stronger warning, or even a boxed warning. The Levine case also involved a malpractice suit against the provider.\textsuperscript{237} When a drug sponsor is aware of malpractice suits or settlements that relate to the risks from the administration of a drug, this information should be available in some form. In the

\textsuperscript{229} See discussion supra Part II.B.2.
\textsuperscript{230} See discussion supra Part V.G.
\textsuperscript{231} See discussion supra Parts III.B.2, C.
\textsuperscript{232} See Preemption Statement, supra note 26, at 3,934.
\textsuperscript{233} Levine v. Wyeth, No. 2004-384, 2006 WL 3041078, at ¶¶ 10–13 (Vt. Oct. 27, 2006) (finding FDA regulation to be minimal when the sponsor proposed a change that the court viewed as different but not stronger, with the FDA stating, with no explanation, that the present labeling should be retained), petition for cert. filed, 127 S. Ct. 2451 (May 21, 2007) (No. 06-1249) (requesting the Solicitor General’s views on granting certiorari).
\textsuperscript{234} For example, the retained warning stated the need to use “extreme care” in the opening sentence. The proposed change did not. See Levine, 2006 WL 3041078, at ¶ 4 n.1.
\textsuperscript{235} Id. at ¶ 6.
\textsuperscript{236} Id. at ¶ 56.
\textsuperscript{237} Id. at ¶ 35 (discussing apportionment of damages between the Health Center and the drug sponsor).
future, drug sponsors may also need to raise whether further surveillance or a risk mitigation strategy is needed.238

The company’s request and the agency’s response seem to have been matters of private communications without any provision for public disclosure. The practice of consultation resembles the petition process discussed below in terms of its effect but without the means to provide public access to the decision in a way that can reinforce the manufacturer’s responsibility and the agency’s accountability. To address these concerns the consultation process should have the safeguards discussed below when the process is intended to have the agency determine that products liability is preempted.

F. Disclosure Determination Petition Process to Balance the Drawbacks of Preemption and FDA Concerns

1. The Role for Petitions

The FDA has justified preemption because of its belief that warnings about unsubstantiated risks would discourage use of beneficial drugs.239 If sponsors could add disclosures without approval by the FDA, warnings would be provided merely to avoid liability.240 Thus, the FDA believes it has a responsibility to ensure the labeling provides sound and useful advice to practitioners about the risks.241

An approach that balances the FDA’s concern over these drawbacks with the need for accountability, reinforcement of the sponsor’s responsibilities, and access would be for the agency to establish a petition process through which the sponsor could request the agency to determine the need for labeling changes about a potential risk. Under this approach, the CBE rule would remain in effect and immediate changes under the existing criteria would continue to be appropriate.

If the sponsor is unsure whether a warning is needed, the sponsor should have the option of filing a petition with the FDA to have the agency both determine what disclosures should be made and confirm that no immediate warning or CBE change is needed.242 The request should be accompanied by an identification of the risk information, the proposed warning or other disclosure, and a description of any additional surveillance or studies believed necessary. If the agency does not act on the matter within a limited time period, the matter should be listed in the physician labeling, or a linked agency web site in a section clearly designated for risk signals. The process would build on that discussed above for disclosing risk signals found

238. See discussion supra Part IV.A–B.1.
239. See Preemption Statement, supra note 26, at 3,935.
240. See discussion supra Part VI.B.1.
241. See Preemption Statement, supra note 26, at 3,935.
242. The FDA regulations already provide for the filing of citizen petitions, 21 C.F.R. § 10.30 (2007). The proposal here would go beyond the existing process by permitting drug manufacturers to file petitions adapted to this circumstance and identifying the support the petition needs and by identifying the subsequent steps involved, including the designation of the matter in the drug labeling or a linked web site as a matter “Under Review.”
in medical reviews. In response to the petition, the FDA would determine whether any warning is needed and whether follow-up studies or monitoring should be done. Requiring the FDA to respond specifically to the petition would increase the agency’s accountability. If the FDA decides that no warning is needed, the labeling or agency web site should reflect the decision.

On the other hand, the sponsors may believe that information about a potentially serious risk from a marketed drug is sensitive information and that the agency should determine its response before any public disclosure is made. This concern may be fueled by the impact public disclosure may have on the drug’s stock market price. This issue again raises the question of whether the FDA is an authoritative gatekeeper for risk information or whether, as this Article suggests, physicians should have access to risk signals about emerging risks under review, such as the ones the VIGOR study on Vioxx indicated, before the agency has completed its deliberations.

Using this petition process can have advantages as well as disadvantages for a drug sponsor. The petition process can provide protection against products liability when used to identify the need for disclosures in the face of uncertainty. The emergence of new issues is illustrated by the agency’s willingness to require a boxed warning based on a meta-analysis of a risk for a marketed drug. While the sponsor may gain protection from liability, the FDA may want the sponsor to provide more information, or even encourage a clinical outcome study to clarify the risk. The caution the FDA required for Vioxx after the results of the VIGOR study were revealed may yet prove a model for a minimally adequate disclosure. That statement acknowledged the unknown significance of the new risk information, the lack of a study to resolve the issue, and the need for caution before use by those most at risk.

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243. See discussion supra Part IV.E.1 (examining disclosures of risk signals found in medical reviews); see discussion supra Part V.G for the agency’s authority to require disclosures.

244. After a period of time, it may be appropriate to provide the information in summary form or in an archive. The web site for the agency’s guidance documents, which includes archived material, may provide a useful format. U.S. Food & Drug Admin., Guidance Documents, http://www.fda.gov/CDER/guidance/ (last visited Oct. 16, 2007).

245. The FDA has the authority to close advisory meetings to the public in certain circumstances. See supra note 40 and accompanying text.

246. See discussion supra, Parts II.B.2, V.E.


248. See Psaty & Furberg, supra note 131 (examining the value of long term-trials).

249. See discussion supra Part II.B–C.

250. See discussion supra Part II.B.3.
2. Effect of Using the Disclosure Determination Petition Process and Its Benefits

When a sponsor uses the Disclosure Determination Petition process to request a determination of the need for a warning, the designation of the matter as under review and the agency's resolution should have preemptive effect and constitute an adequate warning under state law. The process could also lead the sponsor to provide more support for the petition and even make commitments for follow-up monitoring. This process would thus encourage "the industry to act affirmatively... to provide the kinds of information within its control that are the logical postulates of a preemption-worthy federal policy." 251

If the sponsor does not use this petition process, the determination of whether a warning or a change to a warning is warranted under the CBE rule should remain where it has been, along with the potential for products liability. However, the manufacturer may still be able to maintain that a disclosure is preempted under the judicial preemption standards.

If the sponsor has already informed the agency of the underlying risk information, the filing of a specific petition and the agency's review—significant to provide an agency-backed preemption—may seem superfluous. But the petition would have a significant impact: the petition would call the agency's attention to the relevancy of the issue as it relates to tort suits, and the petition would lead to increased public visibility and greater agency accountability. The sponsor would be taking the initiative in identifying the information needed, and, in practice, the agency may have less of a burden in negotiating with the sponsor to obtain a change in labeling. In its petition, the sponsor should address why the statement proposed, as opposed to a stronger warning, is appropriate. Additionally, the public availability of the petition could encourage the sponsor to resolve pending issues with the agency. The trade-off for more protection from liability for the drug sponsor should be greater public availability of information about pending emerging risk issues. This process may appear to give the agency too much leverage; however, the decision to file a petition would remain with the sponsor, and the drug sponsor would continue to receive the procedural protections provided in the law in the event of disputes. 252

3. Relevance of "Fraud-on-the-FDA" Liability and the Petition Process

Another issue is whether tort liability would be imposed, notwithstanding the use of the petition process, if a drug sponsor failed to provide or misrepresented the information that the FDA used for its review. In Buckman Co. v. Plaintiff's Legal Committee, 253 the Supreme Court permitted preemption of a liability claim where

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252. See supra notes 119–20, 124 and accompanying text.
a fraudulent misrepresentation led to the approval of a medical device. The Court concluded that a fraud committed against a federal agency is not a traditional area of state responsibility and that such a theory of liability would impose significant burdens on the agency. The Second Circuit found Buckman not applicable to tort liability cases, a traditional area of state responsibility; however, the matter remains disputed, and the Supreme Court has recently decided to review the issue. The FDA’s Preemption Statement may also create a hurdle for such suits because products liability claims would be preempted “unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning”—a test that suggests that it is up to the FDA to determine the effect of withheld information.

A related issue is whether the availability of tort liability for misrepresentations would “swallow up” any general review process that would otherwise limit liability. The aim of the Disclosure Determination Process, suggested here, is to encourage drug sponsors to raise issues in a transparent way when the need for a warning is not clear and to provide the FDA with information relevant to an informed decision. If the FDA establishes this process, the FDA should address what should happen if a sponsor fails to provide all the information that the FDA identifies as needed or misrepresents the information. The preemption protection should clearly end if the FDA finds these deficiencies. In addition, the preemption protection might also end if the deficiencies and their materiality could be determined in a lawsuit without the need for any agency input with the resource burdens that that would involve. The agency should also consider whether the risk of high punitive damage awards would dissuade sponsors from using the petition process if tort liability could be revived. One possibility might be to consider limits on punitive damages.

254. Id. at 343–44.
255. Id. at 347, 351.
257. Preemption Statement, supra note 26, at 3,936.
258. See Nagareda, supra note 35, at 52; see also Epstein, supra note 35, at 10–14 (discussing various intrusions by tort liability into federal preemption).
259. See generally Philip Morris USA v. Williams, 127 S. Ct. 1057, 1063–64 (2007) (holding that harm to others may not serve as an independent basis for the award of punitive damages and thus retreating from earlier decisions that permitted that factor to be included in the jury’s calculation in awarding punitive damages). Linda Greenhouse, Justices Overturn $79.5 Million in Punitive Damages Against Philip Morris, N.Y. TIMES, Feb. 21, 2007, at A14 (reporting that, while the punitive damages award was overturned on procedural fairness grounds in Philip Morris USA v. Williams, the members of the Court have diverging views on the use of substantive due process to limit punitive damage awards).
260. See Nagareda, supra note 35, at 51–52 (arguing that preemption should create a “bounty for information disclosure by [the] regulated industry” to the FDA and that the prospect for punitive damages serves as a “powerful inducement for investment” by “well-capitalized plaintiffs’ law firms” that undertake mass tort litigation, especially when they can raise a “cover-up” that would “tap into narratives of melodrama”).
G. Overall Assessment of the Disclosure Determination Petition Process

Some may criticize this Disclosure Determination Petition process on several grounds. One concern may be that the process would still unduly reduce the incentive, currently provided by the prospect of products liability suits, for drug companies to respond to safety issues. The listing of a risk as under review may also seem too minor and uninformative to count as a factor that affects preemption. On the other hand, the proposal to list risk reports as under review might be seen as tantamount to a warning, and one that could unnecessarily alarm physicians and discourage beneficial use of the drug. The under review designation, though, is aimed at indicating only that the matter has not been resolved. Another concern could be that the drug sponsor may view the information as confidential information that should not be publicly disclosed until the agency reaches a decision on the need for a warning. However, that position turns on the value of having public access to information about an agency decision when the effect could be to preempt the availability of a traditional remedy for recovery of damages for injuries from drugs. Moreover, the drug sponsor need not use the Disclosure Determination Petition process, choosing instead to rely on the ordinary judicial tests. Despite these criticisms, the approach suggested here has advantages over the other alternatives because it would encourage the drug sponsor and the agency to address through a public process the need for warnings regarding emerging risks in debatable cases.

VII. CONCLUSION

One aim of this Article has been to supplement the authoritative expert model for determining the disclosures that should be made about drugs risks with an access model that provides information about the limits of testing and about emerging risk information. These disclosures should describe the limits of the initial testing, the use of surrogate endpoints for approval, and the status of postmarket testing or postmarket surveillance that may significantly affect safety assessments. In addition, physicians should have ready access to information about risk signals that have been discovered in medical reviews of clinical studies for drugs when approved or when a new use is sought. Providing these disclosures informs the physician of a relevant issue and can encourage the agency to address its significance rather than leaving it unresolved.

The other major concern of this Article is that the agency’s new preemption policy can insulate drug sponsors from products liability in a way that can affect the scope of warnings about emerging risks made on the physician labeling and do so without sufficient public acknowledgment. This Article recommends that the agency change its policy and provide instead that if a drug sponsor seeks a definitive determination by the agency with preemptive effect on the need for a warning, the drug sponsor file a petition with the agency seeking that action. The sponsor’s petition should provide adequate disclosures on the scope of the risk that the sponsor believes exists. The physician labeling, or linked web site, should list
the existence of a petition as being under review until the agency responds to the petition. The agency’s action on the petition would be publicly available.

The proposals made in this Article for disclosures that there are limits to testing and that a petition to determine the need for a warning is under review may be seen as inappropriate. Arguably, such disclosures could lead physicians—out of a concern about potential risks that have not been definitively established—to prescribe fewer drugs that have important benefits. On the other hand, the best evidence to determine the existence of a risk is a controlled study, but the scope of the testing done by the sponsor when the drug is approved is limited, and the available postmarket information may not be sufficient to determine the significance of emerging risks. Assessing the seriousness of the potential risk in this setting involves matters of judgment. But that judgment needs to be publicly exercised to provide the accountability that physicians and users of drugs rightfully expect.

Doctors are trained to be able to balance risks, benefits, and uncertainty. While it is true that disclosing potential safety risks could decrease use of a drug whose benefits may outweigh its risks, not disclosing the existence of risk signals with reasonable support may result in physicians being underinformed about the potential risks of a drug that may outweigh its benefits. The underlying policy choice is between relying solely on the agency as the authoritative decisionmaker to determine the significance of potential risks and providing physicians with access to information about important risk signals.

If the agency’s current preemption policy remains in place, and important risk signals are not disclosed in some manner, there is also the risk that the public may begin to see the agency as a shield that protects the pharmaceutical industry from liability. The expansion of user fees to fund agency personnel and safety-related activities\(^\text{261}\) may also influence the public’s perception about the scale of the industry’s influence over the agency.

A final point should be made about the significance of user fees in shaping the future of FDA regulation. The new law represents the most important expansion of FDA authority since the Drug Efficacy Amendments were signed into law by President John F. Kennedy in 1962.\(^\text{262}\) President George W. Bush, a conservative

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President, signed this law but did so with little ceremony.\textsuperscript{263} While the law strengthens the agency’s substantive authority, the agency’s ability to use that authority in key areas requires further efforts to establish the governing procedures. In practice, the scope of the FDA’s new powers is likely to be determined by the next administration.

The new legislation is a compromise shaped not only by the safety issues raised by the history of Vioxx but also by the periodic need to renew the user fees that provide the major source of funding for the salaries of the agency’s medical reviewers. The division of power between the political parties in Congress and the President will affect whether the renewal of the fees is routine or leads to a reevaluation of the agency’s mission. The FDA, the drug companies, and those in the political branches of the government will inevitably be mindful of the timing and forces that can alter the agency’s mission and powers. The effect of user fees on the regulatory process and the means of providing accountability for major agencies certainly warrants continued study.\textsuperscript{264}

\textsuperscript{263} On the FDA’s web site, there is a picture of the signing ceremony with Secretary Leavitt of the Department of Health and Human Services, Commissioner von Eschenbach of the Food and Drug Administration, and Congressman Joe Barton of Texas standing behind the President. Noticeably absent from the picture are the congressional leaders who actually sponsored the legislation. FDA, Law Strengthens FDA, http://www.fda.gov/oc/initiatives/advance/fdaaa.html (last visited November 6, 2007).

\textsuperscript{264} Margaret Gilhooley, \textit{The Administrative Conference and the Progress of Food and Drug Reform}, 30 \textit{ARIZ. ST. L.J.} 129, 133–35, 140–41 (1998) (summarizing the changes made when user fees were renewed in 1997 and discussing the need for a group like the earlier Administrative Conference to study the impact on the regulatory process of the “funding sunset” represented by user fees).