

Vioxx's History and the Need for Better Procedures and Better Testing

*Margaret Gilhooley**

I. INTRODUCTION

After it was put on the market, Vioxx, a popular and widely-advertised arthritis drug, was found to have cardiovascular risks. It took fourteen months of intense negotiation before a warning was added to the labeling, which cautioned about use by those with heart disease and the “unknown” significance of study findings.¹ When a later study confirmed the risk, Merck, the drug maker, withdrew the drug voluntarily from the market.² The finding of such a serious risk after the drug was on the market and the time it took for a warning to be given, led to a loss of public confidence in the agency³ and a debate about the regulatory system. At the agency’s request, the Institute of Medicine (IOM) of the National Academy of Sciences studied the agency’s regulatory system and issued a report (“IOM Report”) on the future of drug safety, recommending legislative and regulatory changes based on a “vision of a transformed drug safety system” that has “at its core a Lifecycle approach to drug risks and benefits.”⁴

* Copyright Margaret Gilhooley, and Seton Hall Law Review (nonexclusive), 2007. Professor of Law, Seton Hall Law School. I worked in the Chief Counsel’s office for the FDA from 1975 to 1981. Parts of this Article are based on a presentation at the Seton Hall Law Review Drug Symposium on Feb. 16, 2006. I appreciate the library help of Jeanne O’Connor and the research assistance of James Hanley.

¹ See *infra* Part II.

² Alice Dembner, *Maker Takes Vioxx Off Market, Heart Risk Known Earlier Some Say*, BOSTON GLOBE, Oct. 1, 2004, at A1.

³ Becky Bright, *Americans Growing Less Confident in FDA’s Job on Safety, Poll Shows*, WALL ST. J. ONLINE, May 24, 2006, http://online.wsj.com/public/article/SB114831296787359612-16zrHG_MBAihgfzpdzP1YC91kU_20070524.html?mod=blogs.

⁴ NAT. ACAD. OF SCIENCES—INST. OF MED., COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* (2006) [hereinafter IOM REPORT].

The Food and Drug Administration Amendments of 2007 (FDAA) became law shortly before this Article went to the printer.⁵ This Article does not attempt a full analysis of the new legislation. Instead, this Article examines the importance of the procedures governing testing and warnings, a matter Congress has left to the agency to resolve.⁶

This Article begins with a summary of the regulatory history of Vioxx because of its relevance to the debate on procedures and the need for reform. The controversy about Vioxx also led to Congressional hearings,⁷ newspaper coverage and product liability litigation⁸ that have examined the basis for Food and Drug Administration (FDA, or “agency”) decision-making to a degree not usually available. The history is also pertinent because Vioxx exemplified modern drug testing, regulation, and marketing. As has long been known, pre-market tests cannot detect the range of risks users may face, and the existing post-market adverse event reporting system is inadequate to do so.⁹ Vioxx was also engaged in a competitive battle with Celebrex, another arthritis drug made by Pfizer, and both drugs were heavily advertised to consumers on television. Both drugs were also approved by the FDA as priority review drugs that represented a “significant improvement over existing drugs,” a showing that was based on a surrogate endpoint.¹⁰ The approval of drugs on a priority basis also helps the agency meet the timing goals that the FDA accepted when Congress imposed user fees on drug sponsors to permit the agency to hire more reviewers.¹¹ Drugs intended for chronic use, like

⁵ Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 110 Stat. 823.

⁶ *Id.*, sec. 901(a), § 355(o)(3)(F), (4)(d), 121 Stat. 823, 924–25; *see also infra* Part V.

⁷ *See, e.g., FDA’s Drug Approval Process: Up to the Challenge?: Hearing Before the S. Health, Educ., Labor & Pensions Comm.*, 109th Cong. (2005) [hereinafter *Health Comm. Hearing*]; *The FDA, Merck and Vioxx: Putting Patient Safety First: Hearing Before the S. Fin. Comm.*, 108th Cong. (2004) [hereinafter *Finance Comm. Hearing*].

⁸ Anna Wilde Mathews & Barbara Martinez, *E-Mails Suggest Merck Knew Vioxx’s Dangers at Early Stage*, WALL ST. J., Nov. 1, 2004, at A1.

⁹ *See* IOM REPORT, *supra* note 4, at 108–10; *see infra* Part III.

¹⁰ *See* 21 U.S.C.A. § 379h (West 1999 & Supp. 2007) (designating current user fees); FDA White Paper, *Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications* (2005) [hereinafter *Improving Performance in FDA Review*], reprinted in PETER BARTON HUTT ET AL., FOOD AND DRUG LAW 680 (3d ed. 2007).

¹¹ *See* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1840–42 (1996) (finding that changes accompanying the enactment of the user fee legislation led to a change in culture at the agency, which made meeting deadlines “a legitimate measure” of the performance of review officers and their supervisors); Carol Rados, *The FDA Speeds Medical Treatment for Serious Dis-*

Vioxx, may come on the market with limited testing.¹² After a drug is on the market, the sponsor may seek approval for new uses or new claims. Articles may also appear in medical journals about a new use, as they did for Vioxx,¹³ before or without FDA approval, and these medical articles can lead to an increase in the number of prescriptions for the drug for off-label use.

This Article focuses on two changes that are needed in light of this regulatory history. The first is the need for procedures that permit prompt action when the agency seeks warnings about a drug's risks found after marketing. Procedure is power. Providing for more expeditious procedures gives the agency greater ability to protect the public but safeguards are also needed to protect against abuse. The FDA attributed the length of time it took to require a warning for Vioxx to the limits of its authority and to the procedures involved.¹⁴ The present procedures involve formal hearings, but the FDAA provides for other types of dispute resolution that the agency is to determine by regulation and guidance.¹⁵ This Article maintains that the limits of the initial testing and the experimental aspect of drug use are important factors that must be considered in evaluating the fairness and appropriateness of the new procedures.¹⁶

This Article also looks at the desirability of encouraging better drugs. Consideration is needed of proposals to provide non-patent exclusivity for drugs that do long-term outcome testing, as well as for drugs for high-need, high-risk areas, such as the prevention of Alzheimer's disease.¹⁷ In the absence of such testing, the drug label should provide a disclosure of the extent to which drugs approved on a priority basis have been shown by long-term tests to have a significant therapeutic improvement over an identified drug.¹⁸

eases, FDA CONSUMER MAGAZINE, Mar.–Apr. 2006, available at http://www.fda.gov/fdac/features/2006/206_treatments.html (describing priority drugs as those that offer a significant improvement over marketed therapies and reporting that the time for approving a priority drug has decreased since 1990 from twenty-five months to six months)..

¹² See *Finance Comm. Hearing*, *supra* note 7, at 18 (statement of Prof. Bruce Psaty, Univ. of Washington) [hereinafter Psaty Testimony] (stating that at the time of approval only 371 and 381 patients had received doses of 12.5 or 25mg, respectively, for one year or more); see *infra* Part II.D.

¹³ See *infra* Part II.

¹⁴ See *infra* Part III.B.2.

¹⁵ Food and Drug Administration Amendments Act of 2007 sec. 901(a), § 355(o)(3)(F), 121 Stat. 823, 924.

¹⁶ See *infra* Part III.

¹⁷ Alastair J.J. Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 355 NEW ENG. J. MED. 618, 619, 622 (2006).

¹⁸ See *infra* Part V.

To explore these issues, Part II provides a case study of the regulatory history of the FDA's approval of Vioxx and the FDA's regulatory response to the safety issues found with Vioxx. The discussion helps to identify the standards the FDA applies in practice. It also provides examples that can permit evaluation of the need for the statutory changes that have now been made.

Part III provides an overview of some of the changes in how the agency's regulatory experience bears on the agency's authority and on the procedures to require warnings about newly-discovered risk. The discussion notes the reasons risks are found after drugs are approved. This Part also reviews the scope of the agency's existing statutory and procedural authority for seeking labeling changes before the recent legislative changes and summarizes some of the notable testimony on the difficulties with the procedures. The range of views in the FDA's legislative testimony is summarized.

Part IV notes features of key procedural changes in the new legislation. The discussion examines the agency's authority to establish dispute resolution procedures and considers issues for implementation.

Part V explores whether new incentives or disclosures are needed to encourage drug manufacturers to seek initial approval for drugs that have been shown in long-term clinical tests to have a significant therapeutic advantage over existing drugs. This Part considers the proposal to provide non-patent exclusivity as a means to achieve this aim and also suggests that disclosures should be considered about the extent of testing done for priority drugs.

The conclusion in Part VI summarizes the ways in which the regulatory history of Vioxx provides perspective on needed reforms.

II. REGULATORY HISTORY OF VIOXX AND LEGISLATIVE TESTIMONY ON AGENCY AUTHORITY

This Part provides the case study of the steps involved in the FDA's approval of Vioxx and other Cox-2 drugs, and how the agency responded to the information about cardiovascular risks and applied the findings on a class basis when Vioxx was withdrawn because of cardiovascular risk findings. The discussion will also note the specific issues raised by the regulatory history that relate to the debate about the need for statutory changes.

A. *Vioxx and Cox-2 Approval for Pain*

1. Initial Approval for Pain and Arthritis

Vioxx was initially approved for short term acute pain and arthritis in May 1999.¹⁹ The study was a placebo test and thus did not provide any showing that it was better than existing drugs for pain. A number of the studies were short-term studies done to assess pain, but one expert who testified in the congressional hearings did not believe they were adequate to evaluate side effects, such as heart attack, that were common in the population and that may arise from chronic use.²⁰ Celebrex had also been approved for arthritis use.²¹ Both drugs were given priority review by the agency, which led to a faster approval, because, according to an FDA official, “it was hoped and expected that these drugs would provide an important GI [gastrointestinal] safety advantage” although the “agency couldn’t know until [agency officials] reviewed the data.”²²

The FDA approved a statement on special studies in the labeling for Celebrex and Vioxx that there was a reduction of esophageal ulcers compared to other non-steroidal anti-inflammatory drugs (NSAID); however, this was based only on a scope test to examine the esophagus.²³ The labeling contained a warning on the risk of stomach bleeding, and a statement that the correlation between the scope test and the reduction of serious G.I. events with different products “has not been fully established.”²⁴ Merck undertook a study for Vioxx, but no long-term studies were conducted on Celebrex.²⁵

The approvals for these drugs resemble those of fast-track drugs, since the drugs received a faster review, and further testing was

¹⁹ U.S. Food & Drug Admin., Sequence of Events with Vioxx, Since Opening of IND, http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_04_E-FDA-TAB-C.htm. [hereinafter FDA Briefing Materials]. Vioxx and Celebrex belong to the class of drugs known as Cox-2 inhibitors.

²⁰ See Psaty Testimony, *supra* note 12, at 18.

²¹ PHYSICIANS’ DESK REFERENCE 2901 (54th ed. 2000).

²² See *Finance Comm. Hearing*, *supra* note 7, at 60 (statement of Dr. Sandra Kweder, Acting Director of Office of New Drugs, FDA) [hereinafter Kweder Finance Comm. Testimony].

²³ See PHYSICIAN’S DESK REFERENCE 1912–13, 2901–03 (discussing Vioxx and Celebrex, respectively).

²⁴ *Id.*

²⁵ See Barry Meier et. al., *Medicine Fueled by Marketing Intensified Trouble for Pain Pills*, N.Y. TIMES, Dec. 19, 2004, at A38 (noting that “[i]n other words, the world’s best-selling COX-2 [drug, Celebrex,] has never been proved to the F.D.A.’s satisfaction to have the stomach-protecting benefits that originally were supposed to be the point of that category of drugs.”).

needed to confirm the G.I. benefit. However, the agency considered Vioxx to be a priority drug, and did not characterize it as a fast-track drug in the approval letter sent to the company.²⁶

2. Theoretical Cardiovascular Risks

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

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 and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions.²⁷

When Dr. Sandra Kweder testified for the FDA at the Senate Finance Committee about the decision-making for Vioxx, she was asked about why the labeling did not reflect this potential risk. She accepted the characterization that the information was a “theoretical concern” but not “an evidentiary concern.”²⁸ The agency also found “quite reassuring” the safety database for Vioxx, which was larger than that for most drugs, as well as the studies underway, which would be informative because it is “hard to miss a heart attack” in a

²⁶ See U.S. FOOD & DRUG ADMIN., FDA’S REPORT ON NEW HEALTH CARE PRODUCTS APPROVED IN 1999 (1999), <http://www.fda.gov/bbs/topics/ANSWERS/ANS00998.html> [hereinafter FDA 1999 REPORT] (reporting the approval of rofecoxib, the official name for Vioxx, as a priority drug); Second Letter from Robert J. DeLap, M.D., CDER, FDA, to Robert E. Silverman, M.D., Merck Research Laboratories (May 20, 1999), *available at* <http://www.fda.gov/cder/for/appletter/1999/21042ltr.pdf>; *see also supra* Part II.A.1.

²⁷ U.S. Food & Drug Admin., Excerpts from Primary Review of NDA 21-042 Osteoarthritis 9 (1999), *available at* http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_05_F-FDA-Tab-D-1.pdf. Documents found in the litigation that ensued after Vioxx was withdrawn indicated that there was biological evidence that led some Merck scientists to believe by this time there was a theoretical risk. *See* Mathews & Martinez, *supra* note 8; *see also* Psaty Testimony, *supra* note 12, at 18. Professor Psaty stated that

[b]y April 1998, Merck scientists knew of evidence that COX-2 inhibitors such as Vioxx . . . not only lacks the anti-platelet effects of aspirin, but it also disables one of the blood vessel’s main defenses against the clumping of platelets. On the basis of this biologic evidence, it would be reasonable to hypothesize that the treatment of patients with Vioxx might increase the risk of heart attack and stroke compared with either an aspirin-like treatment or with placebo

Id.

²⁸ Kweder Finance Comm. Testimony, *supra* note 22, at 61 (responding to a question from Senator Breaux).

clinical trial. In view of the later studies showing a cardiovascular risk, more attention is needed to determine whether theoretical concerns based on risk signals in clinical trials should be disclosed in some way in the labeling.

B. Review of the VIGOR Study in 2000–04

1. G.I. Benefit and Value of Outcome Studies

The Cox-2 drugs were believed on a theoretical basis to have a gastrointestinal benefit that earlier drugs did not have.²⁹ Merck undertook a clinical outcome study, called the VIGOR study,³⁰ to determine if stomach bleeding is actually reduced in a comparison between Vioxx and naprosyn.³¹ The study results submitted to the FDA for review in March 2000 demonstrated a comparative benefit, but also showed an increased risk of heart attacks and other cardiovascular events at a high fifty milligram dose—this dose was approved only for acute pain relief, but was used in the test to establish a “worst case” estimate of the risk of stomach bleeding, in order to permit a comparison between the drugs for purpose of determining efficacy.³² One lesson is the value of clinical outcome studies in finding a risk, compared to relying solely on surrogate indicators.

2. Cardiovascular Findings and Need for a Cardiovascular Test

After the VIGOR results were received, an FDA advisory committee recommended more studies but not a withdrawal, and the FDA discussed with Merck the possibility of a study especially designed to identify cardiovascular effects.³³ Merck cited ethical and logistical concerns in doing such a study.³⁴ Merck attributed the cardiovascular difference to the ability of naprosyn to reduce risks; the FDA did not

²⁹ See Andrew Pollack, *New Scrutiny of Drugs in Vioxx Family*, N.Y. TIMES, Oct. 4, 2004, at C1.

³⁰ VIGOR stands for “Vioxx Gastrointestinal Outcomes Research.”

³¹ Kweder Finance Comm. Testimony, *supra* note 22, at 50–51.

³² Memorandum from John K. Jenkins, M.D., & Paul J. Seligman, M.D., M.P.H. through Steven Galson, M.D., M.P.H. 5, 9 n.5 (Apr. 6, 2005), <http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf> [hereinafter Decision Memorandum] (noting that Vioxx at the fifty milligram dose was associated with “a hazard ratio of approximately two compared to naproxen based on a composite endpoint of death, MI [myocardial infarctions] or stroke.”).

³³ Alex Berenson et. al., *Retracing a Medical Trail; Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES, Nov. 14, 2004, at A1 (citing Dr. Kweder of the FDA).

³⁴ *Id.* at A32.

accept this protective theory, but was influenced by the lack of a cardiovascular effect in other studies.³⁵ Merck also suggested monitoring cardiovascular results in the ongoing APPROVe trial as an alternative, even though the study was not directed at cardiovascular effects, but rather at whether Vioxx helped prevent colon cancer.³⁶ The failure of Merck to do a cardiovascular study for Vioxx has been a continuing issue among researchers.³⁷ Whether the FDA needs to have more authority to require tests has also emerged as a matter of debate.

3. Negotiation on Cardiovascular Labeling

In 2002, the FDA approved a G.I. benefit claim of Vioxx compared to naprosyn based on the VIGOR study. At the same time, the FDA required labeling about the cardiovascular findings for Vioxx but there has been controversy about the adequacy of the labeling and the process of negotiations that led to the labeling changes. In a Senate hearing, Dr. Sandra Kweder of the FDA testified in connection with labeling changes that “[w]e have to negotiate with the company [about] the specific language of how this should be worded [and regarding] placement.”³⁸ The need for change in the agency’s authority will be discussed later, and while some negotiations between the government and those subject to regulation have a place in a democracy, these particular negotiations seem to have been intense.³⁹

4. Adequacy of Labeling Disclosures

The FDA approved labeling for a G.I. benefit based on the VIGOR study that included under the “Precautions” section of the label a statement that “caution should be exercised when Vioxx is used in patients with a medical history of ischemic heart disease.”⁴⁰ Moreover, at the end of a paragraph with a detailed description of the study’s results at the fifty milligram dose level, the labeling stated that “[t]he significance of the cardiovascular findings from [VIGOR and

³⁵ *Id.*

³⁶ *Id.*

³⁷ See Eric J. Topol, *Failing the Public Health—Rofecoxib, Merck, and the FDA*, 351 *NEW ENG. J. MED.* 1707, 1708 (2004) (describing the use of Vioxx as “an enormous public health issue” and maintaining that the FDA had “the authority to mandate that a trial be conducted, but it never took the initiative.”).

³⁸ *Health Comm. Hearing, supra* note 7, at 23 (statement of Dr. Kweder, Deputy Director Office of New Drugs, FDA) [hereinafter Kweder Health Comm. Testimony].

³⁹ See FDA Briefing Materials, *supra* note 19.

⁴⁰ *PHYSICIANS’ DESK REFERENCE* 2110 (54th ed. 2004).

two placebo studies] is unknown” and that prospective studies on the cardiovascular events “have not been performed.”⁴¹ The description of the VIGOR study also stated that “[t]he VIGOR study showed a higher incidence of adjudicated serious cardiovascular thrombotic events in patients treated with Vioxx 50mg once daily as compared to patients treated with naprosyn”⁴²

The labeling has been described as “tepid” and as having been written in “small print that comes with prescription drugs (and that few actually read).”⁴³ The lack of studies to evaluate the significance of the cardiovascular findings is an important point, and, given the implications, the point should have been more prominent. The labeling suggests, at least to lay readers, that the drug has an unknown potential to cause other cardiovascular risks, perhaps to those without heart disease, or at a lower level. In retrospect, given the results of the APPROVe study, the criteria need to be clearer as to when risks at a high dose level can reasonably be extrapolated to assume that risks exist at lower levels.

5. Need for Earlier Warnings—Existing Approvals

Another criticism of the FDA’s handling of the VIGOR results has been that the FDA should have issued the warnings earlier. Dr. Kweder testified at a Senate hearing that the labeling change took “a very long time” and “much longer than usual” although Merck acted responsibly once the problem was recognized and was trying to collect data from existing studies.⁴⁴

However, an earlier warning would seem to have been especially needed, since the risks found in the VIGOR study did not just relate to a drug that had yet to be marketed. Vioxx was already on the market for acute and chronic pain. This provides an illustration of how the expanding claims for on-market drugs can lead to the discovery of new risks through outcome tests conducted to support the claim.

6. Medical Articles and Off-Label Uses

The risk to existing users may be even greater if a medical journal carries articles about a new use for an existing drug even before the FDA has approved the use, and doctors may start prescribing the

⁴¹ *Id.*

⁴² *Id.*

⁴³ Marcia Angell, *Your Dangerous Drugstore*, N.Y. REV. OF BOOKS, June 8, 2006, available at <http://www.nybooks/articles/19055>. The FDA has since dropped the precaution category as a separate listing.

⁴⁴ Kweder Finance Comm. Testimony, *supra* note 22, at 59.

drug off-label for that new use.⁴⁵ Indeed, in 2000, shortly after the VIGOR results were submitted to the FDA, the *New England Journal of Medicine* (“Journal”) published an article about the study with a Merck scientist as a co-author.⁴⁶ Five years later, the journal repudiated the article, and some have criticized the Journal for failing to correct it even earlier to reflect criticisms of the “naprosyn protective” theory that the FDA had rejected.⁴⁷ A recent report also points out the revenues that can come to medical journals from sales of reprints.⁴⁸

C. *Cardiovascular Findings in 2004 in APPROVe study: Vioxx Withdrawal and Class Relevance for Celebrex and Other Drugs*

1. Study Findings and Vioxx Withdrawal

While Vioxx remained on the market, the FDA and Merck looked to the APPROVe trial to monitor the cardiovascular effects of the drug. The trial was intended to determine if Vioxx helped prevent colon cancer. In fall 2004, before the study was complete, the researchers in this long-term, placebo-controlled trial found a statistically increased cardiovascular risk with a twenty-five milligram dose, the dose level at which Vioxx was prescribed for chronic pain.⁴⁹ Merck reported the findings to the FDA and voluntarily withdrew the drug. Merck regarded the APPROVe study as providing the “first definitive data . . . that demonstrated that there was a higher risk of cardiovascular events” from Vioxx.⁵⁰

2. Public Health Advisory and Relevance for Celebrex

The withdrawal set off public concern about what drug patients should use as an alternative. The FDA issued a Public Health Advisory that recommended limited use of all Cox-2 inhibitors, including

⁴⁵ See *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *vacated*, 202 F.3d 331 (D.C. Cir. 2000) (vacating on procedural grounds); see also Margaret Gilhooley, *Drug Regulation and the Constitution after Western States*, 37 U. RICH. L. REV. 901, 912 (2003) (discussing the impact of the constitutional protections for commercial speech for FDA-regulated products).

⁴⁶ Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520 (2000).

⁴⁷ David Armstrong, *How the New England Journal Missed Warning Signs on Vioxx*, WALL ST. J., May 15, 2006, at A1.

⁴⁸ *Id.* (reporting that the Journal sold more than 900,000 reprints bringing in at least \$697,000 and that Merck bought most of the reprints).

⁴⁹ Decision Memorandum, *supra* note 32, at 3.

⁵⁰ *Finance Comm. Hearing*, *supra* note 7, at 69 (testimony of Raymond Gilmartin, Chairman, President, and CEO of Merck).

Celebrex.⁵¹ The announcement indicated that even long-term use of naprosyn may be associated with an increased cardiovascular risk. An interim recommendation made Celebrex effectively a second choice, since the advisory stated that patients would be “appropriate candidate[s]” for Celebrex when they are intolerant to drugs like naprosyn. The issuance of the press statement and Public Health Advisory also illustrates the significance of the agency’s ability to issue statements about public health problems without advance procedures.

3. FDA Decision Memorandum and Class Effect Determinations—Applicability to Other Drugs

In April 2005, the FDA issued a Decision Memorandum interpreting the available data as “best interpreted as being consistent with a class effect of an increased risk of serious adverse [cardiovascular] events for Cox-2 selective [like Celebrex] and non-selective NSAIDs [like naprosyn].”⁵² Naprosyn also had cardiovascular effects, although at a lesser rate than Vioxx, leading the agency to extend the class beyond Cox-2 drugs to encompass all NSAIDs. The agency did not believe a rank ordering of the drugs within the class was possible given the available data, and thus it recommended a boxed warning for the entire expanded class. The agency recognized that patient variations in response to drugs provided “in part a valid rationale for maintaining a range of options” of NSAID drugs from which patients and doctors may choose.⁵³

Pfizer implemented the FDA recommendation that a prominent boxed warning about Celebrex’s cardiovascular risks be provided on the labeling.⁵⁴ The agency strongly encouraged the company to do a long-term comparative safety study in relationship to naprosyn,⁵⁵ and the company later funded a study that addressed the ethical concerns.⁵⁶ The FDA also identified an interest in a broader type of study

⁵¹ FDA Talk Paper, *FDA Issues Public Health Advisory Recommending Limited Use of Cox-2 Inhibitors*, Dec. 23, 2004, <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01336.html>.

⁵² Decision Memorandum, *supra* note 32, at 2.

⁵³ *Id.* at 11. Maintaining a range of options did not keep the agency from successfully seeking the withdrawal of Bextra, another Cox-2 drug, which had the additional problem of potentially causing life-threatening skin rashes. *Id.* at 12–13.

⁵⁴ *Id.* A National Cancer Institute study also found in December 2004 that Celebrex had a risk of heart disease. See Meier et al., *supra* note 25, at A2; Decision Memorandum, *supra* note 32, at 10 (finding Celebrex and Vioxx “are associated with an increased risk of serious CV events . . .”).

⁵⁵ Decision Memorandum, *supra* note 32, at 16.

⁵⁶ Stephanie Saul, *Pfizer to Finance \$100 Million Safety Study of Celebrex*, N.Y. TIMES, Dec. 14, 2005, at C3. This article reports that the study will examine the safety of the

and stated that the “agency should work closely with sponsors and other interested stakeholders (e.g., [the National Institutes of Health]) to encourage additional long-term controlled clinical trials of non-selective NSAIDs to further evaluate the potential for increased risk.”⁵⁷ Pfizer has also recently resumed consumer advertisements for Celebrex that contain the boxed warnings about Celebrex, naprosyn, and other NSAID drugs.⁵⁸ Interestingly, Celebrex rebounded with two billion dollars in sales and eighteen percent growth in 2006.⁵⁹

4. Earlier Non-Class Finding

The Decision Memorandum made the findings from the APPROVe study on Vioxx applicable to Celebrex without the need for a specific test finding a cardiovascular effect for Celebrex. The effect is presumed unless studies can show otherwise. These findings of a class effect have a powerful impact. Earlier, however, when the VIGOR study first showed a cardiovascular effect for Vioxx, the FDA and an advisory committee considered whether a similar disclosure was needed on Celebrex and decided against it.⁶⁰ The criteria and process for class determinations is an important question. A recent medical journal reported data on a large number of users showing that Vioxx, but not Celebrex, is associated with an increased risk of a first heart attack but that those with a prior heart attack may be at an increased risk if they use either drug.⁶¹

While the agency relied on the clinical testing in requiring the warnings for the Cox-2 drugs, it put little weight on observational tests. The agency reported that its advisory committee members “generally agreed that the observational data could not definitively address the question of a modestly increased [cardiovascular] risk for

drug compared to Naproxen and Ibuprofen in arthritis patients prone to heart attack and stroke, and that some believe that undertaking this study might increase sales by raising consumer confidence in the drug. *Id.*

⁵⁷ Decision Memorandum, *supra* note 32, at 3.

⁵⁸ Alex Berenson, *Celebrex Ads are Back, Dire Warnings and All*, N.Y. TIMES, Apr. 29, 2006, at C3.

⁵⁹ Associated Press, *Pfizer Predicts Earnings Below Expectations and Flat Sales for '06*, N.Y. TIMES, Feb. 11, 2006, at C1; Bloomberg News, *3 Drug Makers Gain as Top Sellers Keep Up Pace*, N.Y. TIMES, Apr. 20, 2006, at C13.

⁶⁰ *In re Bextra and Celebrex Mktg. Sales Practices and Prod. Liab. Litig.*, No. M:05-1699, 2006 WL 2374742, at *3, *7 (N.D. Cal. Aug. 16, 2006) (finding preemption of tort liability based on agency determinations).

⁶¹ *Cox-2 Drugs May Raise Risk of Repeat Heart Attack*, REUTERS, Jan. 29, 2007, <http://www.reuters.com/article/scienceNews/idUSCOL96132120070129> (summarizing a study by Dr. James M. Brophy published in HEART).

the Cox-2 selective compared to the non-selective NSAIDs, with the possible exception of data on [Vioxx] 50mg.”⁶² The role of observational studies and the limits of testing received attention in the congressional hearings.

D. Limits of Testing

The legislative hearing also heard testimony from an expert that the short-term pre-market testing for Vioxx was “not adequate” to detect the potential cardiovascular risks for a drug intended for chronic use and that these risks are “best evaluated” by longer ones.⁶³ On the other hand, a former FDA official testified that small studies serving as the basis for approval are not designed to detect rare adverse events, that “it’s not realistic to increase the size” of the tests to detect rare events, and that improvements are needed in post-approval monitoring and studies.⁶⁴

E. FDA Structure and Role of Observational Studies

The Senate Finance Committee hearing was notable for the criticisms by Dr. David Graham, a director of the FDA Drug Safety Office, who considered the FDA to be “broken.”⁶⁵ He believed that the office responsible for drug approvals had a conflict of interest in evaluating post-market safety risk and was “dominated by a worldview that believes only randomized clinical trials provide useful and actionable information, and the post-marketing safety is an afterthought.”⁶⁶ He complained that his office had no regulatory power and could act only if the office responsible for new drug review agreed.⁶⁷ He criticized the agency for insisting on a statistically significant result before finding a safety risk.⁶⁸ He also endorsed use of observational studies such as one he did on Vioxx with Kaiser-Permanente that was funded by the FDA. In his view, the study

⁶² Decision Memorandum, *supra* note 32, at 7.

⁶³ Psaty Testimony, *supra* note 12, at 18–20.

⁶⁴ *Health Comm. Hearing*, *supra* note 7, at 59 (statement of William B. Schultz, Partner, Zuckerman Spaeder, LLP) [hereinafter Schultz Testimony]. Schultz also stated that “at this time, I personally am not aware of any evidence that FDA made a mistake in approving those drugs.” *Id.* Schultz formerly worked at FDA. *Id.*

⁶⁵ *Finance Comm. Hearing*, *supra* note 7, at 16 (statement of David J. Graham, Associate Director for Science and Medicine, Office of Drug Safety, Food and Drug Administration) [hereinafter Graham Testimony].

⁶⁶ *Id.*

⁶⁷ *Id.*; see Kweder Finance Comm. Testimony, *supra* note 22, at 56 (stating that the authority for final regulatory drug decisions rests with the Office of New Drugs).

⁶⁸ Graham Testimony, *supra* note 65, at 17.

showed 28,000 cases of excess heart attacks were due to Vioxx.⁶⁹ On the other hand, Dr. Kweder of the FDA believed the observational study was of limited value because it did not identify which patients were taking aspirin and whether the Vioxx patients in the study were already at high risk.⁷⁰ The Graham critique has led to proposals for organizational changes that would make determinations of drug safety largely independent of those involved in new drug approvals.⁷¹ However, the focus here is on the procedures to govern the agency's new authority and on the incentives for better testing.

III. AGENCY EXPERIENCE WITH THE LIMITS OF TESTING AND THE IMPACT OF PROCEDURES

This Part examines the agency's general regulatory experience with respect to the procedures that govern the agency's ability to require new warnings about risks that are found after a drug first comes on the market. This examination starts by noting the limits of drug testing and the policy reasons for lessening the rigor of the procedures, namely, that on-market drugs have an experimental quality, since pre-approval testing cannot detect all the risks the user will face. The discussion notes that a less rigorous procedure already exists for fast-track drugs but not for similar priority drugs like Vioxx. Against this background, Part IV provides an overview of the legislative changes that have been made to the agency's authority and the procedures to govern requirements for post-approval testing and warnings.

A. *Limits of Pre-Market Testing and Experimental Aspects of Post-Market Drug Use*

As has long been known, the risks drugs pose cannot be fully known from the testing done before approval. This potential for new risks gives post-market use an experimental aspect that increases the importance of the agency's ability to respond expeditiously when new risks arise. The discussion below illustrates the various ways that the knowledge of post-approval risks is limited.

⁶⁹ *Id.* at 13–15.

⁷⁰ Berenson et al., *supra* note 33, at A1.

⁷¹ See generally Phil B. Fontanarosa et al., *Postmarketing Surveillance—Lack of Vigilance, Lack of Trust*, 292 JAMA 2647 (2004).

1. Early FDA Recognition of Limits of Testing

George Larrick, a former Commissioner of the FDA, pointed out in 1964 that the early period of drug marketing represents “a final step in the testing of the product” and that there is “no way to duplicate fully in clinical trials the great variety” of conditions under which a drug will be used when approved.⁷²

2. Managing the Risk Report

A 1999 FDA Task Force Report (“Task Force Report”) on managing these risks explained the limits of clinical trials and why risks can be found after approval. The size and length of the trials, as well as the similarity of clinical patients needed to determine efficacy, limit the ability to predict the risk when used by the wider population.⁷³ The Task Force Report also described why the agency has confidence in the trials⁷⁴ but also noted measures such as community trials, which could provide additional options to determine risks.⁷⁵ The Task Force Report further recognized that the drug sponsor needs to recoup the costs of drug development, and, as a consequence, manufacturers may roll out new products rapidly after approval.⁷⁶

3. IOM Report on Limits of Testing and a Risk Management Approach

The IOM Report recognized that limitations are “inherent in the system and cannot be changed without adding considerably to the time and expense of drug approvals, which would delay patient access to potentially beneficial drugs.”⁷⁷ The length of the studies is determined primarily by the effort to prove efficacy, and not safety.⁷⁸ The IOM Committee recommended a risk management approach to drug risks and also that Congress ensure that the agency can require clini-

⁷² *Drug Safety: Hearing Before the Subcomm. of the House Comm. on Government Operations*, 88th Cong. 2 (1964) (statement of George Larrick, FDA Commissioner), reprinted in HUTT ET AL., *supra* note 10, at 86.

⁷³ See U.S. Food & Drug Admin., *Managing the Risk from Medical Product Use: Creating a Risk Management Framework* 43–46 (May 1999), <http://www.fda.gov/oc/tfrm/riskmanagement.pdf>.

⁷⁴ *Id.* at 44 (stating that “[c]linical trial investigators expect the majority of severe toxicities to be detected through a combination of high-exposure animal studies and the current profile of trial size and duration.”).

⁷⁵ *Id.* at 45, 50.

⁷⁶ *Id.* at 47–48.

⁷⁷ IOM REPORT, *supra* note 4, at 38.

⁷⁸ *Id.*

cal trials and other measures when needed to match the safety concerns and benefits presented by a drug.⁷⁹

The IOM also emphasized that the existing post-market monitoring of adverse events can detect rare and uncommon serious side effects that are unrelated to the indications for the drug.⁸⁰ However, it is not very effective for detecting a drug's contribution in increasing the frequency of common events.⁸¹ The IOM Report recommended improvements in post-market surveillance that will permit better identification of these risks. These may include use of electronic health insurance records to identify early risk signals.⁸²

B. *Criticisms of the Rigor of the Existing Formal Procedures*

There are considerable hurdles to the agency's existing authority to seek new warnings (including withdrawing a drug through an administrative proceeding or bringing an action in the courts), which has resulted in criticism of the agency in the wake of Vioxx. The discussion here starts by examining the existing procedures and the difficulties they pose.

1. Agency's Existing Authority to Obtain Changes

The agency can withdraw an approved drug from the market if "new evidence of clinical experience" or tests by new methods show that the drug is no longer safe under the conditions of use.⁸³ While the provision does not expressly authorize the agency to require warnings, the agency can indirectly do so by finding that the new information affects the ability to find the drug safe as labeled, or that it makes the label misleading. The withdrawal proceeding, however, is subject to a formal adjudicatory hearing before an administrative law judge.⁸⁴ The administrative proceeding to withdraw drugs is governed by formal hearing, which can be lengthy and resource-intensive. For example, removal of ineffective pre-1962 drugs took thirty years, in part because of the need to provide formal hearings before removal of the drug.⁸⁵ Interestingly, the appellate courts have

⁷⁹ *Id.* at 169–70.

⁸⁰ *Id.* at 108–10; see generally David Kessler, *Introducing MedWatch: A New Approach to Reporting Medication and Device Adverse Effects and Product Failures*, 269 JAMA 2765 (1993).

⁸¹ IOM REPORT, *supra* note 4, at 108–110.

⁸² *Id.* at 114.

⁸³ 21 U.S.C. § 355(e)(2) (2000).

⁸⁴ See *Id.* § 355(e).

⁸⁵ See *Am. Pub. Health Ass'n v. Veneman*, 349 F. Supp. 1311, 1316–17 (D.D.C. 1972) (setting a deadline for the FDA to remove ineffective drugs); see also HUTT ET

become increasingly willing to defer to agency decisions to use informal hearings rather than formal proceedings to resolve administrative disputes when statutes are ambiguous on the need for a formal hearing.⁸⁶

The law also generally prohibits any drug from having misleading labeling.⁸⁷ The agency may bring an action in the courts through the Department of Justice to seize and destroy the misbranded product or to obtain an injunction.⁸⁸ These court proceedings permit a direct remedy without the need for a prior administrative hearing if the lack of warnings makes the product deceptive. The court action must also be brought through the Justice Department or through U.S. Attorneys, and therefore depends upon their willingness to allocate resources to the effort.⁸⁹

2. Legislative Testimony in Vioxx Hearings on Difficulties with Procedures

The Senate hearings on Vioxx identified problems with the existing procedures. Dr. Kweder, the FDA official who testified about Vioxx for the agency, stated her personal view that it would be “very helpful” if the FDA had specific authority to require drug manufacturers to change the labeling to reflect risks, although she recognized that drug companies often will comply with FDA requests for warnings.⁹⁰ A former FDA official also testified to the need for new authority that would allow the agency to require warnings without a de-

AL., *supra* note 10, at 588 (reporting in 2007 that some administrative hearings are still pending or have not been held).

⁸⁶ See *Chem. Waste Mgmt., Inc. v. EPA*, 873 F.2d 1477, 1480–83 (D.C. Cir. 1983); see also RICHARD J. PIERCE ET AL., *ADMINISTRATIVE LAW AND PROCESS* 278–79 (2d ed. 1992) (noting a change in judicial views on the desirability of formal adjudications).

⁸⁷ See 21 U.S.C. § 352(a) (2000).

⁸⁸ See 21 U.S.C.A. §§ 332, 334 (West 1999 & Supp. 2007).

⁸⁹ See Adam Liptak, *For Federal Prosecutors, Politics Is Ever-Present*, N.Y. TIMES, Mar. 18, 2007, at S3 (stating that eight U.S. attorneys were fired, and while they can be removed for any reason, they are “by custom insulated from political changes.”).

⁹⁰ See Kweder Health Comm. Testimony, *supra* note 38, at 79–80 (testifying that “a stronger authority to require changes in labeling would be very helpful”); see also Kweder Finance Comm. Testimony, *supra* note 22, at 54; Gardiner Harris, *FDA Responds to Criticism with New Caution*, N.Y. TIMES, AUG. 6, 2005, at A1 (quoting Dr. Stephen Gelson, Director of the Center for New Drugs at the Food and Drug Administration, with respect to the fourteen months that it took to get the Vioxx label changed that “[w]e’re not proud of how long that took, let me just be clear about that.”).

lay while a challenge is being made.⁹¹ The court proceedings were described as “cumbersome.”⁹² A newspaper report summarized the perception of the constraints on the FDA, noting that the agency “does not own a drug’s label, drug makers do. Short of threatening a seizure if a label is not changed, the agency must negotiate with drug makers over any change. This can lead to delays.”⁹³ On the other hand, an FDA Deputy Commissioner testified that the agency’s existing authority is sufficient and that the “dialogue” between the agency and the company leads to better labeling.⁹⁴

3. IOM Position on Need for New Authority

The IOM found that the agency needs “increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.”⁹⁵

C. *Priority Drugs and Relevance of Procedural Model for Fast-track Drugs*

Before turning to the changes made to procedure in the new law, it is relevant to note that a less rigorous procedure already exists in the law for fast-track drugs, but not for priority drugs like Vioxx,⁹⁶ even though surrogate endpoints may affect the expedited approval of both drugs. The agency should be able to use a more expeditious procedure when drug use has experimental quality and new risks are found.

⁹¹ See Schultz Testimony, *supra* note 64, at 60–63 (maintaining that there is a need for authority to require labeling changes based on new information and to require post-market studies).

⁹² See *id.* at 63 (maintaining that withdrawal proceedings and court actions are “usually inappropriate and cumbersome” and leave the FDA “to negotiate changes” with the company). Seizure actions are also subject to a jury trial on request. See 21 U.S.C. § 334(b) (2000).

⁹³ Harris, *supra* note 90, at A1.

⁹⁴ See *Health Comm. Hearing*, *supra* note 7, at 70 (statement of Scott Gottlieb, Resident Fellow, American Enterprise Institute) (explaining that the “label changes that FDA works on aren’t worded very well” and “the dialogue that goes on between the agency and the sponsor results in much better labeling”). Gottlieb was also a former FDA official. *Id.* at 70.

⁹⁵ IOM REPORT, *supra* note 4, at 11, 168–70.

⁹⁶ See FDA 1999 REPORT, *supra* note 26 (reporting the approval of rofecoxib as a priority drug in less than six months).

1. Fast-track Model, Informal Hearings and Priority Review Drugs

In response to the delays that occurred in the approval of AIDS drugs, the law now allows the agency to approve drugs on a fast-track basis for serious or life-threatening conditions, based on a “surrogate endpoint reasonably likely to predict clinical benefit” without the controlled outcome studies that are traditionally needed.⁹⁷ Approval may be conditioned, however, on the completion of post-approval studies to validate or “otherwise confirm the effect” of the surrogate endpoint.⁹⁸ The agency may withdraw approval of a fast-track drug under “expedited procedures” with an informal hearing when post-market tests required for the drug are not performed or “other evidence” shows that the drug is “not safe.”⁹⁹ Under the present law, though, fast-track status applies only to drugs that the sponsor requests be designated as part of that category.¹⁰⁰

2. Priority Review Drugs Approved on the basis of Surrogate Endpoints

The FDA also expedites approval for Priority Review Drugs that are a “significant improvement” compared to marketed products, which may be with respect to increased effectiveness, reduction of drug reactions, improvements for a subpopulation, or “documented enhancements of patient compliance.”¹⁰¹ The priority status rests on the agency’s inherent authority rather than a specific statutory provision.

The importance of the Priority Review status is illustrated by Vioxx. As Dr. Kweder testified on behalf of the FDA, the drug was initially approved as a priority drug for a routine benefit in pain relief, because the surrogate endpoints showed promise to reduce stomach bleeding.¹⁰² Priority drugs are not subject to the same informal hearing procedures and expanded agency authority that govern fast-track drugs, because the procedures apply only if the sponsor requests fast-

⁹⁷ 21 U.S.C. § 356(b)(1), (2)(A) (2000).

⁹⁸ *Id.* § 356(b)(2).

⁹⁹ *Id.* § 356(b)(3) (providing for expedited withdrawal); *Id.* § 321(x) (defining informal hearing). This proposal relates to the procedures for warnings rather than the other provisions governing fast-track drugs. *Id.*

¹⁰⁰ *Id.* § 356(a)(1).

¹⁰¹ See CENTER FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., MANUAL OF POLICIES AND PROCEDURES § 6020.3 (2007), <http://www.fda.gov/Cder/mapp/6020.3R.pdf>; HUTT ET AL., *supra* note 10, at 708–09.

¹⁰² See Kweder Finance Comm. Testimony, *supra* note 22, at 60; see also FDA 1999 REPORT, *supra* note 26.

track status.¹⁰³ The priority drugs, however, should at a minimum be subject to the informal hearings that govern fast-track drugs. Both priority and fast-track drugs may be approved based on surrogate endpoints, and, as the IOM Report pointed out, initial testing may be sufficient to show efficacy but not long-term safety.¹⁰⁴ Priority drugs should be considered to have an experimental quality when there is limited clinical testing to show safety.

Priority drugs are also significant because the expedited approval for these drugs has been especially important in speeding up the approval of drugs to meet the FDA timing goals—the FDA accepted these constraints when Congress required drug sponsors to pay user fees, which enabled the agency to hire more reviewers.¹⁰⁵ The FDA's goal since 1997 has been to approve ninety percent of priority review drugs within six months.¹⁰⁶

IV. LEGISLATIVE CHANGES ON TESTING, WARNINGS AND ENFORCEMENT, AND OPEN PROCEDURAL ISSUES

Shortly before this Article went to the printer, Congress enacted the FDAA, which makes important changes in a number of areas of FDA regulation.¹⁰⁷ The new law, for example, requires sponsors to have a risk evaluation and mitigation strategy (REMS) to reduce risks when needed to ensure that the benefits of the drug outweigh the risks.¹⁰⁸ The focus here is on the provisions that expand the agency's authority to require post-approval testing and warnings, that strengthen the agency's enforcement powers, and that give the agency the role of resolving the procedures governing certain disputes.

A. *Overview of Post-Approval Testing, Labeling and Enforcement Provisions*

The law authorizes the agency to require a drug sponsor to conduct post-approval studies or clinical studies for a drug (and those in the same class) on the basis of scientific data deemed appropriate to the agency.¹⁰⁹ For an approved drug on the market, the requirement

¹⁰³ 21 U.S.C. § 356 (a)(1)–(2).

¹⁰⁴ IOM REPORT, *supra* note 4, at 124–25.

¹⁰⁵ See Rados, *supra* note 11.

¹⁰⁶ See *Improving Performance in FDA Review*, *supra* note 10, at 680–82.

¹⁰⁷ Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 110 Stat. 823.

¹⁰⁸ *Id.*, sec. 901(a), § 355-1(p), 121 Stat. 823, 926–39.

¹⁰⁹ *Id.*, sec. 901(a), § 355(o)(1), (o)(3)(A), 121 Stat. 823, 922–23.

can only be made based on new safety information.¹¹⁰ A clinical study can be required only if other types of studies are not sufficient.¹¹¹

The drug sponsor can appeal a requirement to conduct a study using “dispute resolution procedures established . . . in regulation and guidance.”¹¹² The new law also authorizes the agency to require safety labeling changes subject to similar dispute resolution procedures.¹¹³ The dispute resolution procedure can be determined by the issuance of a regulation that requires notice of a proposed ruling and an opportunity for comment, which are steps that can take some time.¹¹⁴ While the new law permits the use of agency guidance to establish the dispute resolution procedures, such guidance is now subject to more executive oversight than it was in the past.¹¹⁵ In effect, the search for appropriate procedures is still underway and has been left by Congress to the agency, subject to some constraints.

The new law would also strengthen the agency’s enforcement powers by giving the agency the authority to impose fines or civil money penalties.¹¹⁶ Absent good cause, a sponsor who is in violation of a requirement that there be new testing is subject to a fine,¹¹⁷ as is a sponsor who fails to make a safety labeling change.¹¹⁸ These fines can be substantial—they are not to exceed \$250,000 per violation, but can be doubled for every thirty days of a continued violation, up to \$10,000,000 in a single proceeding.¹¹⁹ A formal hearing before an administrative law judge is still available to assess the fine.¹²⁰

¹¹⁰ *Id.*, sec. 901(a), § 355(o)(3)(C), 121 Stat. 823, 923.

¹¹¹ *Id.*, sec. 901(a), § 355(o)(3)(D), 121 Stat. 823, 923.

¹¹² *Id.*, sec. 901(a), § 355(o)(4)(F), 121 Stat. 823, 925.

¹¹³ Food and Drug Administration Amendments Act of 2007, sec. 901(a), § 355(o)(4)(D)–(F), 121 Stat. 823, 925.

¹¹⁴ *Id.*, sec. 901(a), § 355(o)(4), 121 Stat. 823, 924–26.

¹¹⁵ Exec. Order No. 13,422, 72 Fed. Reg. 2763 (Jan. 18, 2007) (amending Executive Order 12,866 and making guidance subject to executive oversight, similar to the guidance for regulations).

¹¹⁶ *Id.*, sec. 902(b), § 333, 121 Stat. 823, 943.

¹¹⁷ *Id.*

¹¹⁸ *Id.*, sec. 901(a), (b), §§ 355, 355–1, 121 Stat. 823, 922–38; *Id.*, sec. 902(b), §§ 352, 333, 121 Stat. 823, 943.

¹¹⁹ *Id.*, sec. 902(b), § 333(4)(A), 121 Stat. 823, 943.

¹²⁰ 21 U.S.C.A. § 333(g)(3)(B) (West 1999 & Supp. 2007).

B. Factors in Assessing an Appropriate Procedural Framework

1. Mathews v. Eldridge Balancing Test

The balancing test used for procedural due process helps identify the considerations that can play a role both on a legal and policy basis. That test looks at the private interest affected, the risk of error, and the public interest.¹²¹ The test is case-specific, and the Supreme Court of the United States gives some deference to the governmental choice.¹²² The issues in the hearings are likely to involve scientific and policy judgments rather than credibility issues, but the agency's approach may be criticized as being ad hoc, a point raised in the IOM Report.¹²³

In determining the proper balance, one factor that would make the public health interest particularly strong is when new risks are found for drugs that have an experimental aspect. As noted above, the initial period of drug use can be seen as the final phase of drug testing.¹²⁴ Moreover, there may be less information available on the safety risks of priority drugs and other drugs approved on a faster basis because of surrogate endpoints.¹²⁵ The need to protect the public justifies having an expeditious procedure when the issue involves the need for new safety warnings—especially so when the risks emerge for an on-market drug, where use has an experimental quality given the limited ability of pre-market testing to discover risks.

If the agency seeks to require a post-market clinical test as with Vioxx, the burdens of performing the test make the private interest stronger. If there is a public health hazard, however, and the testing is not adequate to determine the scope of the risk, the public interest also weighs strongly. Of course, a warning about the lack of the testing may be another alternative to protect the public, an approach the FDA used with the VIGOR warning for Vioxx—but again, some believe that warning to have been insufficient.¹²⁶

2. Options for Consideration

The law already provides for the use of informal hearings for fast-track drugs if evidence demonstrates that the drug is not safe or if

¹²¹ See *Mathews v. Eldridge*, 424 U.S. 319, 334–35 (1976).

¹²² *Id.* at 331.

¹²³ IOM REPORT, *supra* note 4, at 123.

¹²⁴ See *infra* Part II.A.

¹²⁵ IOM REPORT, *supra* note 4, at 124–125.

¹²⁶ See *supra* Part II .B.4.

the sponsor fails to complete post-approval studies.¹²⁷ Informal hearings are clearly preferable to formal hearings for many disputes,¹²⁸ and they represent one option for the new dispute resolution process. Other types of dispute resolution procedure are possible, so long as they maintain a fair balance among the relevant interests. An informal determination before an independent decision-maker may be another option. The dispute resolution process sought may even be one that seeks to persuade directly the officials who can approve the drug without establishing a record for review. In determining the balance, due weight should be given to all the factors, including both the need to protect the public health and any experimental aspects related to the drug use.

3. Relevance of Enforcement Stage

Another factor in assessing the procedural system is whether it should be viewed as a two-stage process—an initial dispute resolution and an enforcement hearing. The leading due process case considered by the Supreme Court involved a two-step process for calculating the fairness of the determination.¹²⁹ The dispute resolution and enforcement stages in the new law warrant further examination.

There may be questions about how the two stages interrelate. For example, will the dispute resolution process receive any weight at the enforcement hearing, or will the issues be decided *de novo*? Will the dispute resolution be considered a final decision, and one that is open to immediate judicial review?¹³⁰ Postponing judicial review, however, increases the incentive for the company to comply. The company's ability to obtain review will also be stronger if the issues are purely legal, or if they relate to constitutional standards.¹³¹ Will the hearing on the fine be solely concerned with whether a violation occurred, or will it consider whether a test or warning was needed? Will the administrative law judge's ability to take into account "such other matters as justice may require" in determining the amount of

¹²⁷ 21 U.S.C. § 356(a)(3) (2000).

¹²⁸ See *supra* Part III.B.

¹²⁹ See *Mathews v. Eldridge*, 424 U.S. 319, 334–35 (1976); see generally Jerry L. Mashaw, *The Supreme Court's Due Process Calculus for Administrative Adjudications in Mathews v. Eldridge: Three Factors in Search of a Theory of Value*, 44 U. CHI. L. REV. 28 (1976).

¹³⁰ See *Abbott Labs. v. Garner*, 387 U.S. 136, 139–48 (1967) (discussing pre-enforcement review); see generally *Ticor Title Ins. Co. v. FTC*, 814 F.2d 731 (D.C. Cir. 1987) (discussing the test for finality).

¹³¹ See, e.g., *Abbott Labs.*, 387 U.S. at 137–38.

the fine encompass review of the need for the requirement?¹³² If there is further review at the enforcement stage, will this affect the procedures needed at the initial dispute resolution stage and the availability of pre-enforcement review? The availability of a formal hearing can also influence the Court in finding that an administrative proceeding to impose money penalties satisfies other Constitutional requirements.¹³³

Overall, the procedural changes relieve the agency of having to use formal hearings and can permit a more expeditious resolution. While the agency's authority has been strengthened, in practice the agency and sponsor may still resolve the close issues through negotiation, which should move faster now. After all, neither the agency, the industry, nor the public want to see a repeat of what went wrong with Vioxx. But having a fair procedure to test these issues is still important and has now been left by Congress to the agency to determine.

V. INCENTIVES AND DISCLOSURES TO ENCOURAGE BETTER INITIAL TESTING

This Part suggests that economic incentives and better disclosures may be necessary to encourage manufacturers to perform clinical and comparative testing to show that a drug has a significant therapeutic advantage over the existing standard of care. The limits of the pre-market testing for drugs make it important to consider ways to achieve better initial testing or post-market testing that is promptly completed. There also are other benefits in having drugs with that kind of support. One way to obtain such testing would be for Congress to require it, but that is unlikely because it would delay the availability of the drugs. Another approach that has been raised is to provide non-patent economic incentives if the testing is done.

A. *Need for Better Testing*

Long-term clinical tests provide the best evidence about the safety risks of drugs for chronic use, as the history of Vioxx indicates. However, as the IOM pointed out, "clinical trials are designed pri-

¹³² See 21 U.S.C.A. § 333(g)(3)(B) (West 1999 & Supp. 2007).

¹³³ *Commodity Futures Trading Comm'n v. Schor*, 478 U.S. 833, 848–52 (1986) (finding that an administrative proceeding with a formal hearing that adjudicated counterclaims for money reparations did not intrude into the judicial function of Article III courts); *Atlas Roofing Co. v. Occupational Safety and Health Review Comm'n*, 430 U.S. 442, 461 (1977) (upholding administrative proceeding to impose fines as not being in conflict with the right to a jury trial).

marily with efficacy,” not safety outcomes in mind.¹³⁴ If a drug sponsor obtains initial approval for a drug based on easy-to-prove claims for a chronic use like pain relief, as occurred with Vioxx, the testing will have less ability to surface long-term safety problems.¹³⁵ Another benefit of better initial testing is that it would encourage companies to seek FDA approval for the drug’s most important use. Also, initial testing will make it less likely that significant uses will be reported instead in a medical journal by the sponsor, leading to off-label use without FDA review.¹³⁶ Finally, it is desirable to have drugs provide significant benefits, rather than simply be a minor variation of other drugs.¹³⁷ The FDA, however, cannot require comparative studies absent a claim by the manufacturer and cannot deny approval of a safe and effective drug simply because it provides a routine benefit.¹³⁸

B. Incentive Proposal to Meet Testing Needs

1. Proposal in the New England Journal of Medicine

A proposal by Dr. Alastair Wood would use non-patent incentives to encourage the development of better drugs, including long-term post-market safety testing for drugs like Vioxx.¹³⁹ The drugs would be approved on the same basis as they are now, but an added period of exclusive marketing would be available if testing was done with an FDA-approved design showing that the drug was safer than the standard therapy.¹⁴⁰ If the tests were not completed on time, the extended exclusivity would be lost. The proposal would also offer incentives to encourage drug sponsors to develop drugs meeting important medical needs such as the prevention of chronic diseases. For high-risk and high-need drugs, approval could be obtained based on surrogate indicators, but additional exclusivity would be available if the endpoints were converted to clinically meaningful endpoints by post-market testing.¹⁴¹

¹³⁴ IOM REPORT, *supra* note 4, at 38.

¹³⁵ Psaty Testimony, *supra* note 12, at 18.

¹³⁶ See *supra* Part II.B.6.

¹³⁷ See MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES 240 (2004).

¹³⁸ See HUTT ET AL., *supra* note 9, at 527.

¹³⁹ Wood, *supra* note 17, at 619.

¹⁴⁰ *Id.* The study could show equivalence to the existing therapy but would have to have an adequate ability to determine comparability. *Id.* at 620.

¹⁴¹ *Id.* at 621.

2. Implementation Option

The Hatch-Waxman amendments to the food and drug laws provide a research incentive of three years of market exclusivity for post-approval clinical investigations to support any new use of a drug, significant or otherwise.¹⁴² These provisions might be adapted to provide incentives for better testing to demonstrate safety and a significant comparative advantage. The incentive would be greater if the drug were initially approved based on clinical trials showing that the drug had a therapeutically significant advantage over existing drugs. To encourage timely completion of studies conducted post-market, the maximum exclusivity would be reduced the longer it took to complete the study post-approval. The scope of the exclusivity is, of course, important and might be eighteen months in length. This period is half the length of the three-year Hatch-Waxman research incentive for marketed drugs, but it would be stronger if tacked onto the end of the patent term and also barred all generic approvals.¹⁴³

3. Downside

This proposal has a significant downside, since the exclusivity would delay the availability of less expensive generic forms of the drug. There are also risks that a new incentive will be unduly expanded and have loopholes and unintended consequences. But in looking at the history of Vioxx overall, a larger question is whether reform should only deal with improving the agency's procedures and authority to require tests and improve post-market surveillance, as important as these goals are. We should also consider whether it is possible to get drug sponsors to seek approval from the beginning or soon thereafter for a drug that represents an important health advance and has the best form of testing. If this is possible, it would result in a better drug upon initial approval, as well as a better generic form.

¹⁴² See 21 U.S.C.A. § 355(j)(5)(F) (West 1999 & Supp. 2007).

¹⁴³ The exclusivity only protects the new use of the drug which allows doctors to prescribe the drug off-label for its original use. The law also provides a five-year exclusivity for a new chemical entity, but the incentive has "relatively limited significance" because it runs from the date of FDA approval and is likely to expire before the patent. See Elizabeth H. Dickinson, *FDA's Role in Making Exclusivity Determinations*, 54 FOOD & DRUG L.J. 195, 200 (1999) (stating that exclusivity bars FDA approval for a five year period beginning from the date of approval of the first NDA); Bruce Kuhlik, *The Assault on Intellectual Property*, 71 U. CHI. L. REV. 93, 98 (2004).

C. *Disclosure of the Limits of Testing Priority Drugs and Chronic Use Drugs*

Disclosures may have a useful role in encouraging better testing if the incentive approach is not adopted. Priority drugs are approved on an expedited basis because they are expected to offer a significant improvement over marketed therapies.¹⁴⁴ Early approval is available because of the prospect of a comparative benefit over other drugs.¹⁴⁵ Even though the FDA cannot mandate a relative efficacy showing as a basis for approval, when sponsors seek a priority review because a drug represents a significant improvement over existing treatment, the labeling should reflect the extent to which a significant improvement over an identified therapy has been established in FDA-approved clinical tests. Doing so could spur the completion of full tests, as well as the type of testing necessary to show whether the drug has a special medical benefit that justifies early approval.¹⁴⁶ The FDA could also differentiate between priority drugs that represent major therapeutic advances¹⁴⁷ and ordinary priority drugs that meet the present criteria, allowing the agency to identify the drugs that will receive faster attention for reviews. This distinction would be a reasonable basis for determining the agency's priorities.¹⁴⁸

VI. CONCLUSION

This Article examined the regulatory history of Vioxx, since it is likely to continue to serve as a benchmark for assessing what changes are necessary to make drugs safer. One lesson from that history is the need for change in the formal procedures that have, until now, governed the agency's ability to require new warnings or tests. Though the Food, Drug and Cosmetic Act already provides informal hearings for disputes when new risks are found for fast-track drugs, these procedures did not apply to Vioxx, a priority drug approved on an expedited basis, because the sponsor did not request fast-track status.¹⁴⁹

¹⁴⁴ See Kweder Finance Comm. Testimony, *supra* note 22, at 60; HUTT ET AL., *supra* note 10, at 708–10.

¹⁴⁵ HUTT ET AL., *supra* note 10, at 691 n.4.

¹⁴⁶ There can be complications in providing these disclosures, which is illustrated by the “special statement” the FDA allowed for Vioxx and Celebrex. See *supra* Part II.A.

¹⁴⁷ See Wood, *supra* note 17, at 622.

¹⁴⁸ See Margaret Gilhooley, *Addressing Potential Drug Risks: The Limits of Testing, Risk Signals, Preemption and the Drug Reform Legislation*, 59 S.C. L. REV. (forthcoming Dec. 2007) (offering more discussion on disclosures of risks).

¹⁴⁹ See 21 U.S.C. § 356(a)(2) (2000).

The case for a less rigorous procedure for requiring new warnings is especially strong when the drugs have undergone limited testing, and the risks are identified by the adverse experiences of the drug users or by post-market surveillance. The initial post-market use of the drug has an experimental quality that needs to be taken into account in developing procedures. The new law gives the agency specific authority to require post-approval tests and warnings and the authority to impose fines for violations; the agency, however, has been left the discretion to determine the dispute resolution procedures for the new testing and warning requirements.¹⁵⁰ In assessing the fairness of the scheme the agency adopts, the experimental nature of the drug risks should be recognized as a major consideration that supports a flexible and expeditious process for requiring warnings.

Consideration should also be given to the drawbacks of the safety testing initially done for Vioxx. A proposal has been made to provide non-patent economic incentives to encourage better long-term comparative post-market testing for determining safety and benefits.¹⁵¹ This approach warrants Congress's attention. When drugs are approved on a priority basis, as many are, they are supposed to represent a significant improvement over existing therapy. The agency should require disclosures when these advantages are not shown by adequate comparative clinical testing.¹⁵²

Drug reform is an important public concern. Drug risk cannot be eliminated, however, and new risks will inevitably be discovered after a drug is on sale. The current legislative efforts provide the agency with more authority and more flexible procedures to address the risks discovered after the drug is on the market. The new amendments ease the agency's enforcement burdens, and the change signals to the public, the industry, and the agency, that Congress wants more forceful action when significant safety risk issues emerge, and that Congress will hold the agency and the industry accountable if that action is not taken.

¹⁵⁰ See *supra* Part IV.A.

¹⁵¹ See Wood, *supra* note 17, at 623.

¹⁵² See *supra* Part V.