

TRANSPARENCY AND INNUENDO: AN ALTERNATIVE TO REACTIVE OVER-DISCLOSURE

SCOTT M. LASSMAN*

I

INTRODUCTION

Transparency has become the new watchword in public policy and political debates about pharmaceuticals. From medical journal editors to the U.S. Food and Drug Administration (FDA), stakeholders have called for increased transparency of pharmaceutical research and safety information in the wake of recent, well-publicized safety issues with some drug products.¹ For example, the American Medical Association (AMA) approved a resolution in 2004 recommending the public registration of all clinical trials at inception, with the results from these trials then made publicly available through either journal publication or an electronic data repository.² Bills proposing similar registration and disclosure requirements for ongoing and completed clinical trials have been introduced in Congress and in several states.³

The pharmaceutical industry is firmly committed to the transparency of clinical research and safety information. Although additional improvements in risk communication undoubtedly can and should be made, it would be a mistake to overlook the significant progress to increase transparency achieved to date by the pharmaceutical industry. In 2002, for example—well before the current debate over transparency erupted—the Pharmaceutical Research and Manufacturers of America (PhRMA), a trade organization representing the innovative pharmaceutical industry, adopted the *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* (PhRMA

Copyright © 2006 by Scott M. Lassman

This Article is also available at <http://law.duke.edu/journals/lcp>.

* Assistant General Counsel, Pharmaceutical Research and Manufacturers of America.

1. Erika K. Lietzan, *Clinical Trials Registries & Clinical Trial Results Databases: An Update*, UPDATE: FOOD AND DRUG LAW, REGULATION, AND EDUCATION, Sept.–Oct. 2005, at 9, 9–12.

2. See Press Release, American Medical Association, AMA Offers Guidelines for Clinical Trial Registry (Sept. 9, 2004), available at <http://www.ama-assn.org/ama/pub/category/13949.html> (outlining initial guidance provided by AMA on five elements of the registry).

3. E.g., Fair Access to Clinical Trials Act of 2004, S. 2933, 108th Cong. (2004); H.R. 5252, 108th Cong. (2004); Assemb. B. 72, 2005 Leg., Reg. Sess. (Cal. 2005); B. 6870, 2005 Assemb., Reg. Sess. (N.Y. 2005); B. 4637, 2005 Assemb., Reg. Sess. (N.Y. 2005). In least one state—Maine—a proposed bill has been signed into law. Leg. Doc. 1618, 122nd Leg., 1st Spec. Sess. (Me. 2005) (codified at ME. REV. STAT. ANN. tit. 22, § 2700-A (2005)).

Principles).⁴ Among other things, the *PhRMA Principles* clearly state the industry's commitment to the "timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing, *regardless of outcome*."⁵

The *PhRMA Principles* were revised in June 2004 to better clarify when clinical trial results would be made public.⁶ Four months later, PhRMA established a centralized electronic database to facilitate the public's access to clinical trial results, particularly unpublished study results.⁷ In addition to the approved labeling, the database is intended to contain citations or links to published journal articles reporting on clinical studies of the drug in question, as well as summaries of unpublished studies in a standardized, non-promotional format.⁸

Although transparency generally benefits the public health, it presents risks when taken to extremes. Countervailing and equally legitimate interests must be balanced against transparency when implementing any public policy on the disclosure of clinical trial and safety information. For instance, disclosure policies that fail to protect proprietary research data could undermine competition and curtail incentives for innovative research, thereby ultimately harming the public health. Likewise, policies that require the disclosure of very preliminary data of unknown significance also pose public health risks. Such information is the scientific equivalent of rumor and innuendo and, particularly when disseminated by a public health agency like FDA, risks confusing or misleading healthcare providers and patients about the true risks and benefits of drug products. Thus, although transparency is an important goal, it must be pursued in a balanced manner that accommodates other legitimate public health interests.

This tension between transparency and other public health interests has become particularly acute in debates about the disclosure of clinical trial information and the creation of publicly available, searchable databases. Physician groups, medical journal editors, pharmaceutical manufacturers, state governments, the Institutes of Medicine, and even the World Health Organization, have all entered the fray.⁹ However, as these debates about clinical trial information disclosure have been raging, the transparency issue has

4. PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, *PRINCIPLES ON CONDUCT OF CLINICAL TRIALS AND COMMUNICATION OF CLINICAL TRIAL RESULTS* [hereinafter *PhRMA Principles*] (2002).

5. *Id.* at 20 (emphasis added).

6. *PhRMA Principles* (2004) (revised principles), available at <http://www.phrma.org/publications/publications/2004-06-30.1035.pdf>.

7. See *PhRMA Clinical Study Results Database*, <http://www.clinicalstudyresults.org/about/> (indicating the database will include both "published articles and unpublished study summaries"). The database itself is available at <http://www.clinicalstudyresults.org> and is intended to provide a "one-stop shop" for clinical trial information on drug products that have been approved in the United States. *Id.*

8. *Id.* As of May 2006, the database contained information on over 250 different prescription drug products and thousands of separate clinical trials. *Id.* (last visited May 2, 2006).

9. Lietzan, *supra* note 1, at 9.

quietly emerged in another venue: FDA. In May 2005, FDA announced it was planning to create a “Drug Watch” website that would communicate information about the safety of drug products at a very early stage,¹⁰ sometimes even before FDA had made a decision about the relevance (or lack thereof) of the reported information.

This article examines the tension between transparency and other public health interests in the context of FDA’s proposed Drug Watch website. It argues that although the FDA proposal seeks to achieve a laudable goal—the prompt communication of important and useful safety information about drug products to physicians and patients—it fails to properly balance transparency and other legitimate public health interests. As a result, the Drug Watch website, if finalized, likely would (1) disseminate unverified and potentially misleading safety information; (2) prompt physicians and patients to make healthcare decisions based on little more than scientific innuendo; and (3) undercut well-established methods of risk communication, such as the approved drug label. This article then proposes an alternative to this type of reactive overdisclosure, suggesting that a more balanced and effective method of risk communication would be to use the Drug Watch website as part of an accelerated labeling-revision process, which would provide valid and useful safety information in a more timely manner.

II

FDA’S PROPOSED DRUG WATCH WEBSITE

On May 10, 2005, FDA published a draft guidance document in the Federal Register proposing to create a “Drug Watch” website.¹¹ According to FDA, the goal of the website is “to share emerging safety information before [FDA has] fully determined its significance or taken final regulatory action”¹² The website would be available as a discrete section of the existing FDA website.¹³

According to the draft guidance document, FDA would use three factors to decide whether and when to post “emerging” safety information on the Drug Watch website:

- (1) whether the information could significantly affect prescribing decisions or how patients should be monitored;
- (2) whether measures can be taken based on emerging safety information that could help to prevent or mitigate harm; and

10. 70 Fed. Reg. 24,606 (May 10, 2005).

11. *Id.*

12. CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA’S “DRUG WATCH” FOR EMERGING DRUG SAFETY INFORMATION 2 (2005) [hereinafter FDA DRUG WATCH] (Draft Guidance), available at <http://www.fda.gov/cder/guidance/6657dft.pdf>.

13. *See id.* at 1 n.3 (indicating location of Drug Watch page).

(3) whether an unapproved use of the drug appears to pose a significant risk to patients.¹⁴

The draft guidance document also provides numerous examples of the types of “emerging” safety information that would be communicated under the proposal.¹⁵ Most of these examples meet the three criteria listed above. For example, FDA states the website will include information about “an important risk minimization procedure . . . put into place by a sponsor in response to emerging information.”¹⁶ Likewise, FDA indicates that the Drug Watch program could be used to disseminate information about significant emerging risks that FDA believes are associated with a drug product, such as when a drug product has been linked to serious skin reactions in patients allergic to eggs.¹⁷ Importantly, these examples involve safety information that is valid and useful.

In these examples, the website’s safety information is “emerging” only in the sense that it is newly acquired, not in the sense that it is still under investigation. One of the examples that FDA offers, however, does involve information that is still under active investigation. According to FDA, the Drug Watch website will contain “factual information about newly observed, serious adverse events,”¹⁸ such as post-marketing reports of renal failure in elderly patients, even before a causal relationship between the adverse reaction and the drug product has been established.¹⁹ Recognizing that the reliability of this information is unknown, FDA proposes to accompany the information with a disclaimer along the following lines: “This information reflects FDA’s preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this webpage when additional information or analyses become available.”²⁰ FDA calls this preliminary information “emerging *potential* safety issues.”²¹

The Drug Watch proposal was intended to blunt criticism by Congress and the media that FDA had been too slow to inform physicians and patients about safety issues associated with several classes of drug products, including selective serotonin reuptake inhibitors and Cox-II inhibitors. The Drug Watch proposal thus represents a significant departure from FDA’s current practice of risk communication, which generally takes place only after the validity and significance of the information have been adequately demonstrated and which

14. *Id.* at 5.

15. *See id.* at 2–3 (proposing that newly observed adverse events associated with a drug, risks that can be avoided through proper patient selection, and important risk minimization procedures will be disseminated to the public).

16. *Id.* at 3.

17. *Id.*

18. *Id.* at 2.

19. *Id.* at 3.

20. *Id.*

21. *Id.* (emphasis added).

relies primarily upon label changes and other official regulatory actions such as “Dear Doctor” letters to inform physicians about new safety information.²²

The proposed Drug Watch website, if implemented, would certainly provide physicians and the American public with reams of safety information much earlier in the process. What is less clear is whether any of this additional information will be useful.

III

THE DANGERS OF TOO MUCH TRANSPARENCY

The underlying goal that FDA is seeking to achieve through the Drug Watch program—the prompt communication of important and useful safety information to physicians and their patients—is laudable.²³ Most aspects of the Drug Watch program achieve this goal. For example, FDA proposes to disseminate information when “an important risk minimization procedure is put into place by a sponsor in response to emerging information.”²⁴ Prompt communication of this type of valid safety information is important because it can be used in a meaningful way by physicians to guide prescribing and treatment decisions.

Other aspects of the Drug Watch program, however, raise serious public policy and legal concerns because they seek to publicize information that is too vague and preliminary to be of any value in making informed treatment and prescribing decisions. These aspects of the program take transparency to an extreme and ignore other legitimate public health interests, such as the importance of validating information before it is disseminated to ensure that it is accurate, useful, and not misleading. Although transparency should be vigorously pursued as a public policy objective, it must be balanced against other important public policy objectives. The Drug Watch proposal fails to achieve such a balance.

A. The Utility of Publishing Safety-Related Information

Safety-related information published on the FDA website should be robust enough—that is, with a strong enough basis—to be useful to physicians and the public in guiding prescribing and treatment decisions. This principle seems self-evident from a public policy perspective and is in fact reflected in the FDA criteria for deciding whether to post information on the Drug Watch site.²⁵

22. KATHLEEN M. MAZOR ET AL., PHARMACOEPIDEMIOLOGY AND DRUG SAFETY, COMMUNICATING SAFETY INFORMATION TO PHYSICIANS: AN EXAMINATION OF DEAR DOCTOR LETTERS 1–2 (2005), <http://www3.interscience.wiley.com/cgi-bin/fulltext/110438560/PDFSTART>.

23. FDA DRUG WATCH, *supra* note 12, at 2.

24. *Id.* at 3.

25. *See id.* at 4–5 (discussing how FDA will determine which drugs and information will be included on the Drug Watch website).

Moreover, it has also been codified as a legal requirement by the Consolidated Appropriations Act of 2001 (the Act).²⁶

The Act established a floor for the reliability of information publicized by federal agencies, requiring that federal agencies ensure the maximum in quality, objectivity, utility, and integrity of the information they disseminate.²⁷ To implement the Act, the Office of Management and Budget (OMB) issued policy and procedural guidance applicable to all agencies covered by the Act.²⁸ In furtherance of the Act and the OMB Guidelines, the Department of Health and Human Services (HHS) also adopted individual guidelines²⁹ that contain a specific section applicable to FDA.³⁰ Among other requirements, the OMB Guidelines and the HHS Guidelines mandate that information disseminated by FDA have one important attribute: utility.³¹ According to the HHS Guidelines applicable to FDA, “We only disseminate information that we believe will be useful to the public or a segment of the public.”³²

The requirements of the Act are particularly important for information published on the Internet, such as FDA’s proposed Drug Watch website. In its agency-wide guidelines, OMB cautions that the Internet raises unique concerns: “[T]hat the Internet enables agencies to communicate information quickly and easily to a wide audience not only offers great benefits to society, but also increases the potential harm that can result from the dissemination of information that does not meet basic information quality guidelines.”³³

In developing the draft guidance,³⁴ it appears that FDA failed to take into account the Act’s requirements and the special considerations raised by publication of information of this type on the Internet. Although much of the information FDA intends to publish would provide meaningful guidance to patients and healthcare providers, other information will be so preliminary as to

26. See Pub. L. No. 106-554, sec. 10978, § 515(a), 114 Stat. 2763, app. at 153–54 (2000) (LEXIS) (requiring guidelines to ensure proper dissemination of information by federal agencies).

27. See *id.* at app. 154 (mandating that federal agencies “issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information . . . disseminated”).

28. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, 67 Fed. Reg. 8452, 8458 (Feb. 5, 2002) [hereinafter OMB Guidelines].

29. See Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by Health and Human Services Agencies, 67 Fed. Reg. 61,343, 61,343 (Sept. 30, 2002) (announcing availability of guidelines).

30. FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, GUIDELINES FOR ENSURING THE QUALITY OF INFORMATION DISSEMINATED TO THE PUBLIC, pt. II, sec. F (2003) [hereinafter HHS GUIDELINES], available at <http://aspe.hhs.gov/infoquality/Guidelines/index.shtml>.

31. OMB Guidelines, *supra* note 28, at 8458–59; HHS GUIDELINES, *supra* note 30, at pt. II, sec. F, § V(A).

32. HHS GUIDELINES, *supra* note 30, at pt. II, sec. F, § V(A). The OMB Guidelines likewise provide that the usefulness of information to its intended users must be considered in assessing the overall quality of information to be disseminated by an agency. OMB Guidelines, *supra* note 28, at 8458–59.

33. *Id.* at 8452.

34. See generally FDA DRUG WATCH, *supra* note 12.

be meaningless. The draft guidance document even acknowledges that in some cases FDA will publish information on the Drug Watch website before the agency has assessed its meaning, significance, or potential consequences.³⁵ For example, FDA will publicize that it is evaluating a particular product before it is able to make a tentative conclusion as to the significance of the information³⁶—meaning also before it is possible to provide any guidance to health care practitioners or patients concerning actions that should or should not be taken as a result of the information. Furthermore, FDA indicates that the following statement is appropriate for publication on the Drug Watch website: “FDA is investigating postmarketing reports of renal failure in elderly patients treated with Drug A, but a causal relationship has not been established. We are continuing to analyze these reports to determine whether the occurrence of these events affects the risk/benefit assessment of Drug A therapy.”³⁷

Such a general statement provides no meaningful information about the drug. It does not assist patients or health care practitioners in assessing the conditions, if any, under which Drug A therapy is appropriate or inappropriate for a particular patient. Simply put, health care practitioners and patients cannot be expected to use such a statement in any meaningful way when FDA itself—with full access to all adverse experience reports and the data in the New Drug Application (NDA)—cannot yet discern the meaning, significance, or potential consequences of the underlying information.

By contrast, FDA provides examples elsewhere in its draft guidance of other types of information about drugs that can rationally inform treatment decisions because the data and conclusions reflect a greater degree of certainty about the risk or means of reducing the risk associated with the drugs in question.³⁸ For example, the draft guidance discusses a situation with Drug C in which the sponsor has determined the drug product can cause organ damage and has issued recommended steps to be taken before and during drug therapy to minimize this risk.³⁹ This type of specific advice is useful to physicians and the public. Similarly, the hypothetical circumstances involving Drug B posit a situation in which FDA has concluded that the drug is associated with certain adverse reactions in a specific patient population and thus can provide meaningful information to physicians by ensuring their increased level of awareness with respect to use of that drug with that population.⁴⁰

Moreover, the examples for Drugs B and C are consistent with the factors FDA states it will use when deciding whether to post information on the Drug

35. *See id.* at 1–2 (indicating FDA intends to disseminate information before it has completed a full evaluation).

36. *See id.* at 1 (noting the Drug Watch website will identify drugs “for which FDA is actively evaluating early safety signals”).

37. *Id.* at 3.

38. *See id.* (illustrating situations in which the Drug Watch website will contain information about risks that are believed to be associated with a drug but that can be avoided).

39. *Id.*

40. *Id.*

Watch website. In particular, FDA states it will consider posting information when (1) “new and emerging safety information could significantly affect prescribing decisions or how patients should be monitored” or (2) “measures can be taken as a result of [the new] information that could help to prevent or mitigate harm.”⁴¹ These are useful benchmarks for deciding when publication of safety information is appropriate and in fact reflect the principle embodied in the Act that information disseminated by FDA should be robust and useful.⁴² Indeed, if FDA carefully applies these two factors, it should publish safety information only after it has conducted an evaluation sufficient to determine whether there is a valid association between the health hazard and the drug, thus enabling it to offer specific recommendations to the public.

Preliminary information of the type discussed in the Drug A example would not meet either of these criteria, so such information should not be posted on the Drug Watch website or even discussed as an option in FDA’s draft guidance.⁴³ Because the information is preliminary and its significance unknown, it could not and should not have any effect on rational prescribing decisions, nor could it be used to help prevent or mitigate harm. On the contrary, there is a very real risk that the information could itself *cause* harm by encouraging patients to modify or discontinue their safe and effective drug therapy.

B. The Risks of Too Much Transparency

The problem of too little transparency—failure to communicate known risks about a drug product—can cause serious harm to the public health. This is the problem FDA is attempting to address with its Drug Watch proposal. However, the premature communication of “preliminary” safety information also entails serious public health risks, since physicians and patients may make health care decisions based upon information that later turns out to be wrong. This is the problem of too much transparency.

The FDA Drug Watch proposal threatens too much transparency because it essentially calls for a “data dump” of safety information at a very early stage, prior to any determination that the events are associated with the drug product in question and before it is possible to provide any guidance to physicians or the public.⁴⁴ This information is not only of little or no help in guiding prescribing or treatment decisions, but it is also potentially misleading when presented on an official FDA Drug Watch website. Indeed, regardless of the disclaimers

41. *Id.* at 5.

42. See Consolidated Appropriations Act of 2001, Pub. L. No. 106-544, sec. 10978, § 515(b)(2)(A), 114 Stat. 2763, app. at 154 (2000) (LEXIS) (requiring guidelines that ensure and maximize quality, objectivity, utility, and integrity of information).

43. As discussed earlier in this section, the Drug A example provides a hypothetical illustration of a publication of preliminary observations of adverse events associated with a particular drug. FDA DRUG WATCH, *supra* note 12, at 2–3.

44. See *id.* at 3 (noting that information will be made available to the public while FDA is still in an evaluating stage).

used, such information is likely to be confusing at best and unduly alarming at worst, perhaps prompting patients who are being treated safely and effectively with a medication to discontinue their drug therapy. And, even more potentially dangerous, many are likely to do so without consulting a physician.

In addition, due to malpractice concerns, some physicians may be unwilling to prescribe products listed on the Drug Watch website. Thus, patients may be switched to alternative therapies not listed on the Drug Watch page that have more common or more serious, known risks than the “potential” risks identified on the Drug Watch page. This outcome could have a far greater impact on public health than any risk stemming from the unsubstantiated safety signal.

The risks associated with premature disclosure of safety information are especially acute when the speaker is a public health agency such as FDA. Information disseminated by FDA is routinely picked up by the press and widely reproduced.⁴⁵ There is little doubt that breaking information about the safety of marketed drug products published on FDA’s Drug Watch website will receive intense media attention. Indeed, informing and educating the public is a primary goal of the website. Regardless of any disclaimers or qualifying language used in the product-specific postings, physicians and the general public are likely to view postings on the Drug Watch website as official regulatory judgments about the safety of the listed products.

For this reason, any information about drug safety that FDA communicates to the public must be robust and reliable. In cases in which the FDA evaluation has progressed to the point where the safety information has been confirmed as reliable or where it is possible to offer guidance to help avoid or reduce risks, FDA can rationally conclude that the potential benefits of posting the information outweigh any potential harm. In all other cases, the risks associated with publishing “preliminary” information outweigh the potential benefits.

Even when safety information is valid, FDA should make efforts to stress the importance of consulting a physician before modifying or discontinuing treatment. New safety information about a particular medication—even when confirmed as valid—may be alarming to many patients. A prominent reminder by FDA to “always consult your physician before modifying or discontinuing treatment with [a medication listed on the Drug Watch website]” will help to ensure that patients do not unilaterally stop taking safe and effective medicines.

In addition, FDA should strive to ensure that safety information posted on the Drug Watch website is placed into proper context. Posting risk information alone without relevant benefit information may be misleading. The lack of balancing, positive information, such as the approved indications or other benefits for physicians or patients to consider, could negatively affect treatment decisions for serious diseases. It is therefore critical to explain in detail not only

45. See, e.g., Rob Stein, *FDA Considers Warnings for Eczema Creams*, WASH. POST, Feb. 12, 2005, at A09.

the new safety information, but also the offsetting benefits of continued drug use, the comparative risks of discontinuing medication either with or without a physician's consent, and the range of possible treatment alternatives. A link to the approved package insert may be appropriate. This information will better enable patients and their health care providers to make informed decisions concerning treatment.

C. The Importance of Drug Product Labeling

The Federal Food, Drug and Cosmetic Act (FDCA) and FDA's implementing regulations establish labeling as the primary means of communicating information about a prescription drug product, including safety-related information such as warnings, contraindications, precautions, and adverse reactions.⁴⁶ The FDA Drug Watch website would undermine the role of labeling as the most important source of valid safety information.

Under the regulatory scheme envisioned by the FDCA, safety-related information is evaluated in consultation with the applicant in the context of an NDA and is incorporated into labeling, both before and after approval of the NDA.⁴⁷ The FDCA enables FDA to withdraw approval of an NDA if: (a) scientific data show that the drug is unsafe for use under its recommended conditions of use; (b) new evidence shows that the drug has not been shown to be safe for use under conditions of use upon the basis of which the application was approved; or (c) based upon new information, FDA determines that the labeling of a drug is false or misleading, including the failure to reveal a material fact, and the labeling is not corrected within a reasonable time after the sponsor receives notice of the matter.⁴⁸

Accordingly, with respect to safety issues that arise after approval, when new information indicates that the labeling—including the safety-related sections—is no longer complete or accurate, sponsors must revise the labeling or face withdrawal of the approval of the NDA.⁴⁹ By regulation, FDA requires that labeling be revised to include new warnings “as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been prove[n].”⁵⁰

Many provisions of the FDA draft guidance are consistent with the principle that labeling should remain the most important source of valid safety information. For example, FDA proposes to publish new safety information about an “important risk minimization procedure” put into place by the drug

46. *See, e.g.*, Federal Food, Drug, and Cosmetic Act, 21 U.S.C.S. § 355 (2003) (designating guidelines for new drug applications); 21 C.F.R. § 201.57(e) (2005) (requiring revisions for labeling).

47. 21 U.S.C.S. § 355.

48. *Id.* § 355(e).

49. *Id.*

50. 21 C.F.R. § 201.57(e). FDA's regulations also provide a means for the agency to require inclusion of certain emerging safety information in prescription drug advertising. *See* 21 C.F.R. § 202.1(j) (2005) (establishing procedures for situations in which little information has been publicized about drugs that might be potentially dangerous).

sponsor, or about certain adverse reactions in a specific patient population that FDA has concluded are causally associated with a particular drug product.⁵¹ Since this information is critical for the safe use of the product, it either would be reflected in the approved labeling via a supplemental application or would already be consistent with that labeling. The Drug Watch website can and should be used to publicize this type of important safety information more quickly and more broadly than might be possible with a labeling change.

However, if implemented, other provisions of the FDA draft guidance would undermine the primacy and usefulness of labeling. In particular, FDA states that it will post “emerging safety information before [it has] fully determined its significance or taken final regulatory action.”⁵² In other words, FDA intends to publish safety information that goes beyond that contained in the FDA-approved labeling and that might never be incorporated into such labeling. Revisions to labeling based upon review of data and information submitted in accordance with FDA’s regulations provide the appropriate and statutorily mandated vehicle for the agency to ensure that patients and health care practitioners have access to current and scientifically valid benefit-risk information. By circumventing this established communication mechanism, the Drug Watch program would serve only to undercut the reliability of labeling and introduce confusion into the healthcare and patient communities.

The Drug Watch program could also ultimately result in incorporating questionable safety information into approved drug labeling. Although Drug Watch postings are intended to be a “heads up” to health care professionals, today’s litigious medical environment nearly guarantees that Drug Watch warnings will be used by plaintiffs’ attorneys as “proof” of material safety risks. Moreover, courts might also allow the warnings as evidence of causation. Juries, however, are unlikely to appreciate the complex distinctions between a Drug Watch alert and other forms of regulatory action. This could well lead to physicians practicing defensive medicine based on unverified safety signals, an outcome that is not necessarily in the best interest of patients. It is also possible that some sponsors, in defense of anticipated litigation, may elect to make labeling changes on the basis of a Drug Watch posting. If the ultimate decision is that there is no new safety concern, the labeling could contain inappropriate precautions that could limit patient access to the benefits of drug treatment.

Publicizing dubious safety information is particularly troubling because it runs counter to ongoing efforts by FDA to ensure that risk communication is focused on the most important safety information. For instance, FDA recently issued a final regulation that reorganizes the approved physician labeling for drug products to include a “Highlights of Prescribing Information” section identifying the most important safety and effectiveness information.⁵³ Likewise,

51. FDA DRUG WATCH, *supra* note 12, at 3.

52. *Id.* at 2.

53. Requirements for Prescription Drug Product Labels, 71 Fed. Reg. 3922 (Jan. 24, 2006) (codified at 21 C.F.R. pt. 201).

FDA has suggested that the “brief summary” for direct-to-consumer print advertisements should include only the most important risk information,⁵⁴ since “exhaustive lists of minor risks distract from and make it difficult to comprehend and retain information on the more important risks.”⁵⁵ Yet the FDA Drug Watch website would flood physicians and consumers with preliminary safety information of unknown significance, making it even more difficult for them to comprehend and retain information on important—and known—risks.

FDA states it intends to use the Drug Watch website to disseminate “important” emerging safety information.⁵⁶ If safety information is “important” such that it (a) “could significantly affect prescribing decisions or how patients should be monitored” or (b) “could help to prevent or mitigate harm,”⁵⁷ *it should be in the labeling*. The goal of the Drug Watch website, therefore, should be to publish safety information that is robust enough to be included in the approved labeling but that is disseminated in a more widespread and timely manner than could be achieved with a typical labeling revision. This means limiting the use of the Drug Watch website to an accelerated label revision process.⁵⁸

D. The Necessity of Communication Between FDA and the Sponsor

The FDA draft guidance does not make any provision for input from sponsors but instead indicates that FDA will “notify” the sponsor “shortly before” information is posted on the Drug Watch website.⁵⁹ The failure of FDA to consult with sponsors on all emerging safety issues prior to posting is a major weakness with the Drug Watch website proposal.

FDA and the drug sponsor each have relevant scientific data and information on individual drugs and each has a responsibility to assure that relevant, scientifically valid, and useful information is disclosed to health care practitioners and made available to patients. Sponsors typically have the greatest access and familiarity with data—both emerging and historical—on their drug products. Sponsors’ contributions could include critical information such as new adverse event reports that are still in the processing cycle or knowledge about ongoing or unpublished studies that may further substantiate or refute the issue. Accordingly, sponsor input is invaluable in determining the meaning and relevance of potential safety signals as quickly as possible, and, if

54. Draft Guidances for Industry on Improving Information about Medical Products and Health Conditions, 69 Fed. Reg. 6308 (Feb. 10, 2004).

55. CENTER FOR DRUG EVALUATION AND RESEARCH ET AL., FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, BRIEF SUMMARY: DISCLOSING RISK INFORMATION IN CONSUMER-DIRECTED PRINT ADVERTISEMENTS 2 (2004) (Draft Guidance), available at <http://www.fda.gov/cder/guidance/5669dft.pdf>.

56. FDA DRUG WATCH, *supra* note 12, at 1.

57. *Id.* at 5.

58. *See infra* Part IV.

59. *Id.* at 6.

warranted, developing an appropriately worded communication that accurately describes the available information.

In addition, sponsors need sufficient prior notice to respond appropriately to questions about the posted information from physicians, the media, other regulatory authorities, and the general public. Because of the global nature of the Internet and the status of most sponsors as large multinational corporations, it is highly likely that regulatory authorities, health care providers, and media in other countries will contact the local sponsors for information regarding Drug Watch postings. Drug sponsors need prior notice of Drug Watch postings to prepare for these questions and to notify regulatory authorities and foreign affiliates as appropriate. Drug sponsors should not first learn about a Drug Watch posting from the media or concerned physicians; they should hear about it from FDA well prior to the posting.

This lack of an opportunity for constructive input prior to publication is compounded by the chilling effect of FDA's warning that "[r]epresentations made to minimize the effect of emerging risk information on the site may also be considered false or misleading."⁶⁰ In other words, the sponsors who typically have the most complete information are cautioned not to take issue with the appropriateness of the admittedly preliminary information, which may ultimately be shown to have no clinical or regulatory significance.

FDA justifies this lack of meaningful prior notice on the basis of the need for haste with respect to dissemination of emerging safety information.⁶¹ But if that information is by definition too preliminary to support a labeling change or other more formal communication, it is difficult to understand how FDA can justify finding that publication of the information is too urgent to allow a reasonable opportunity to consult with the sponsor.

In light of the potential harm to the public health resulting from inappropriate publication of emerging safety information, excluding sponsors from the evaluation process cannot be justified. Any risk communication mechanism adopted by FDA should include specific procedures for soliciting sponsor input on the critical questions of when there is sufficient knowledge about an emerging safety issue that publication would be useful to the public, and therefore appropriate, and how this emerging safety information should be conveyed.

E. The Problem with Publishing Information Requiring a Disclaimer

The draft guidance indicates that when FDA publishes information that is still under evaluation, a disclaimer will accompany the information.⁶² The agency does not commit to specific disclaimer language, but offers the following

60. FDA DRUG WATCH, *supra* note 12, at 7.

61. *See id.* at 2 (indicating that information will be distributed earlier than in the past because patients and physicians increasingly rely on this information to make prescribing and treatment decisions).

62. *Id.* at 3.

example of one that might be published: “This information reflects FDA’s preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this webpage when additional information or analyses become available.”⁶³ The draft guidance does not address where or how prominently the disclaimer language would appear.⁶⁴

This part of FDA’s proposal is rather startling and raises the question of why FDA is publishing information that requires a disclaimer. If a disclaimer of this sort is required, the information is by definition too preliminary and questionable to be useful. Indeed, such a disclaimer is a tacit admission that the information cannot and should not be used to guide rational prescribing or treatment decisions. Rather than attempt to correct potentially misleading information with a disclaimer, FDA should simply refrain from disseminating such information until a disclaimer is no longer required.

IV

A PROPOSAL FOR IMPLEMENTING THE DRUG WATCH WEBSITE IN A BALANCED MANNER

The ultimate goal of FDA’s proposed Drug Watch program should be to ensure that meaningful safety information is disseminated to the public in a timely manner. Nobody is clamoring for quick access to preliminary information that may be untrustworthy or misleading, least of all physicians responsible for the health of their patients. Yet that is exactly what the Drug Watch website, as currently envisioned, would provide.

FDA should take its own advice and focus on disseminating information that (a) “could significantly affect prescribing decisions or how patients should be monitored” or (b) “could help to prevent or mitigate harm.”⁶⁵ This would limit the information published on the Drug Watch site to that which is robust and useful. FDA already has identified some examples of information that meet these criteria in its draft guidance document, such as new risk management programs or new safety information that FDA has determined to be associated with a drug product.⁶⁶ In addition, a third type of information could be disseminated under the Drug Watch program in place of the currently proposed “preliminary” safety information: safety information in appropriate cases as part of an accelerated label-review process.

Pharmaceutical companies typically do a good job of ensuring that drug labeling is current and reflects the most up-to-date and accurate safety information available. Companies promptly disclose information and work diligently with FDA on the content and placement of new safety information in

63. *Id.*

64. *Id.*

65. *Id.* at 5.

66. *See id.* at 2–3 (providing examples of the types of information FDA plans to publish).

the approved labeling.⁶⁷ Complex emerging data may require very careful review, analysis, and interpretation before an appropriate labeling statement can be developed. It should be recognized that this process can take time. Historically, FDA has worked well with companies to ensure that reliable new safety information is provided to healthcare professionals in a timely manner.⁶⁸ On rare occasions, however, this process can become protracted.

The Drug Watch website could be used as part of an accelerated label revision process to ensure that valid, new safety information is communicated as quickly as possible. In particular, when the complexity of the data and its interpretation indicate that a lengthy review process can be anticipated, a timeline could be established for continuing discussions between FDA and the sponsor. If a label change is not finalized at the end of this timeline, the Drug Watch website could be used to disseminate the safety information while labeling discussions continue. Once the labeling is revised, however, the Drug Watch listing should be removed or revised accordingly.

This process would ensure not only that important new safety information is communicated in a timely manner to physicians and the public, but also that (1) such information is robust, validated, and useful; (2) sponsors have a meaningful opportunity for input; and (3) the approved labeling remains the primary means for disseminating safety information. In short, it would achieve the goals of transparency while also balancing a number of other important public health interests.

67. All manufacturers of prescription drug products are required to submit reports to FDA of adverse events associated with the use of their products. See 21 C.F.R. §§ 310.305, 314.80 (2006). Adverse events that are “serious and unexpected”—meaning that the event is serious and is not listed on the approved drug label—must be reported to FDA within fifteen days of the initial receipt of the information by the manufacturer. Moreover, the manufacturer must promptly investigate these “serious and unexpected” adverse events and submit follow-up reports within fifteen days of receiving new information. All other adverse events must be reported to FDA at quarterly intervals for the first three years after the date of approval and annually thereafter. FDA also requires manufacturers of approved drug products to submit an annual report within sixty days of the anniversary date of approval. 21 C.F.R. § 314.81 (2006). The annual report must contain, among other things, a summary of “significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product.” 21 C.F.R. § 314.81(b)(2)(i). In addition, the annual report must contain both published and unpublished reports of “new toxicological findings” in animal and *in vitro* studies (for example, animal studies bearing on the cancer risk of the drug). 21 C.F.R. § 314.81(b)(2)(v). Finally, the annual report must include any new clinical studies of the approved drug product, regardless of whether the study is published or unpublished. 21 C.F.R. § 314.81(b)(2)(vi). The failure to make these reports is considered to be a “prohibited act” subject to all available remedies under the Federal Food, Drug, and Cosmetic Act. 21 U.S.C. § 331(e) (2000). It also is grounds for withdrawal of approval of the application. 21 U.S.C. § 355(e) (2000).

68. For drug and labeling changes information, see U.S. Food and Drug Administration, Index to Drug-Specific Information, <http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm> (last visited May 27, 2006).

V

CONCLUSION

In summary, although many aspects of the proposed Drug Watch program are valuable, those provisions that seek to disseminate preliminary information of unknown significance or utility, especially without sponsor involvement and discussion, should be abandoned. Such information is not validated, not useful for guiding rational prescribing decisions, and not likely to accomplish anything other than confusion among physicians and patients as well as irrational fears about the safety of drugs on the list, which is detrimental to the public health. Moreover, as described above, the dissemination of such information is inconsistent with federal law governing the disclosure of safety information by the government.⁶⁹

The Drug Watch website can be a valuable tool for physicians and patients if it promptly communicates validated safety information that can be used in a meaningful way by physicians to guide prescribing and treatment decisions. Such information should complement the approved labeling rather than undercut it. In this regard, the Drug Watch website may be useful as part of an accelerated labeling revision process in certain circumstances to ensure that new, valid information is communicated in a timely manner.

69. See Consolidated Appropriations Act of 2001, Pub. L. No. 106-544, sec. 10978, § 515(b)(2)(A), 114 Stat. 2763, app. at 154 (2000) (LEXIS) (requiring guidelines that ensure and maximize quality, objectivity, utility, and integrity of information).