



August 8, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2005D-0062, FDA Request for Comments on the Draft Guidance entitled, "FDA's 'Drug Watch' for Emerging Drug Safety Information" 70 Federal Register 24606 (May 10, 2005)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments on the Draft Guidance published by the Food and Drug Administration (FDA) on May 10, 2005 concerning the "Drug Watch" program (Draft Guidance). PhRMA is a voluntary, non-profit trade association that represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer and more productive lives. The large majority of new prescription medicines approved for marketing in the United States are produced by PhRMA member firms. Accordingly, PhRMA and its member companies have a significant interest in the provisions of the Drug Watch program and its potential significant impact upon public health and therapeutic decision-making. PhRMA's detailed comments are set forth below.

I. Executive Summary

PhRMA fully endorses 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. Most aspects of the Drug Watch program achieve this goal. For example, PhRMA supports FDA's proposal to disseminate information on its Drug Watch site when "an important risk minimization procedure is put into place by a sponsor in response to emerging information." Draft Guidance at 3, lines 103-04. 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. While manufacturers typically disseminate this type of information themselves through labeling changes and other mechanisms (e.g., Dear Doctor letters), PhRMA fully supports FDA's role in ensuring that this information is promptly and broadly disseminated on its Drug Watch website.

One aspect of the Drug Watch program, however, raises serious public policy and legal concerns because it seeks to publicize information that is too vague and preliminary to be of any value in making informed treatment and prescribing decisions. For example, FDA proposes to post information about adverse events at a very early stage, prior to any determination that the events are associated with the drug product in question. This information not only is of little or

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no help in guiding prescribing or treatment decisions, but also is potentially misleading when presented on an official FDA Drug Watch website. Indeed, regardless of the disclaimers used, such information is likely to be at best confusing and at worst unduly alarming, prompting many patients who are being treated safely and effectively with a medication to discontinue their drug therapy -- often without consulting a physician.

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. PhRMA shares that goal and believes it can be achieved by adhering to the following basic principles:

- Safety-related information published on FDA's website should be robust enough to be useful in guiding prescribing and treatment decisions;
- Safety-related information published on FDA's website should not create undue alarm among patients or encourage patients to alter or discontinue their current therapy without first consulting a physician;
- Labeling should continue to be the primary vehicle for communicating safety-related information to the public, and the Drug Watch website should complement labeling;
- FDA should seek timely comment as to the appropriateness of the information from the sponsor of the application in question prior to publishing information on the Drug Watch website; and
- FDA should not disseminate the type of preliminary information of unknown significance that requires a disclaimer.

While many provisions in the current Draft Guidance meet these criteria, others would result in the dissemination of unconfirmed, unusable, and potentially misleading information about drug safety. As discussed in Section II below, PhRMA believes that the dissemination of this type of preliminary safety information of unknown significance is contrary to the public health. Moreover, as discussed in Section III below, the dissemination of such preliminary information appears to be inconsistent with federal law, including the Federal Data Quality Act and Section 705 of the Federal Food, Drug, and Cosmetic Act.

If despite these public policy and legal issues, FDA nevertheless decides to disseminate preliminary safety information under the Drug Watch program, FDA should address several issues to mitigate the public health concerns. In particular, FDA should, among other things: (a) better define the threshold for publishing preliminary safety information; (b) revise the disclaimer to better communicate the relevance of the posted information; and (c) improve the mechanism for revising and removing posted safety information. These issues are discussed in more detail in Section IV below.

In sum, PhRMA fully supports appropriate risk communication but believes any risk communication program adopted by the Agency must assure the quality and appropriateness of both the information conveyed and the vehicle used to disseminate the information. It is in this spirit that PhRMA offers the following specific comments and recommendations to assist the Agency in revising the Drug Watch program.

II. The Dissemination of Preliminary Safety Information of Unknown Significance Is Contrary To the Public Health

A. Safety-Related Information Published by FDA Should be Useful to Healthcare Professionals and the Public in Guiding Prescribing and Treatment Decisions

PhRMA believes that any safety-related information published on FDA's website should be robust enough to be useful to physicians and the public in guiding prescribing and treatment decisions. Much of the information FDA intends to publish would provide meaningful guidance to patients and healthcare practitioners, but the Draft Guidance also indicates that FDA intends to post information on the Drug Watch website very soon after potential safety signals are first identified, when little is known or understood and no useful information is available.

The Draft Guidance states that FDA will publish some information on the Drug Watch webpage before the Agency has assessed its meaning, significance, or potential consequences. Indeed, according to the Draft Guidance, FDA will publicize the fact that it is evaluating a particular product before the Agency is able to make even a tentative conclusion as to the significance of the information and before it is possible to provide any guidance to healthcare practitioners or patients concerning actions that should or should not be taken as a result of the information. By way of example, 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.

See Draft Guidance, Section III., page 3, lines 85-88.

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

In contrast, elsewhere in the Draft Guidance, FDA provides examples of other information that can rationally inform treatment decisions because it reflects a greater degree of certainty about the risk and/or means of reducing the risk. The example provided for Drug C reflects a situation in which the sponsor has determined that the drug product can cause organ damage and has issued recommended steps to be taken before and during drug therapy to minimize this risk. This type of specific advice is useful to physicians and the public, and PhRMA fully supports publicizing such sponsor findings and recommendations. Similarly, the example provided for Drug B posits a situation in which the Agency has concluded that the drug is associated with certain adverse reactions in a specific patient population and thus can provide meaningful information to physicians. PhRMA fully supports dissemination of this type of information as well.

In this regard, PhRMA supports the first two factors identified in Section III.B. of the Draft Guidance that FDA expects to consider when deciding which drug products and information to post on the Drug Watch website. In particular, FDA states that it will consider posting information when: (a) new 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.” Draft Guidance, Section III.B, page 5, lines 153-54, 158-59. PhRMA agrees that these factors are relevant when deciding whether or not the Agency should publicize potential safety information. Indeed, PhRMA believes that careful consideration and application of these two factors will result in publication of safety information only after the Agency has conducted an evaluation sufficient to allow it to determine whether there is causation or a valid association and thus to offer specific recommendations to healthcare professionals and the public.

Preliminary information of the type discussed in the example of Drug A, however, would not meet either of these criteria and thus should not be posted on the Drug Watch website. 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 (as discussed further below) that the information could itself *cause* harm by encouraging patients to modify or discontinue their safe and effective drug therapy without a valid reason. FDA thus should clarify that it will not publish this type of “potential” safety information but instead will rely upon the two factors discussed above, which ensure that published safety information is valid and meaningful.

B. FDA Must Consider the Harm Caused by Premature Publication of Potential Safety Issues

In adopting a risk communication program, it is essential that the Agency carefully consider the significant harm that could be caused by premature publication of potential safety signals. Information published on the Drug Watch website will be picked up by the press and widely disseminated. Indeed, that is the primary goal of the website. Regardless of any disclaimers or qualifying language used in the product-specific postings, PhRMA believes that

physicians and the general public will necessarily 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 where the Agency's 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 contrast, FDA's plan to publicize the fact that it is evaluating a particular product before the Agency is able to make even a tentative conclusion on causation and before it is possible to provide any guidance to the public is particularly troubling. Such information will, at best, cause confusion among physicians and patients and, at worst, cause undue alarm, prompting many patients to modify or discontinue their medications, often without consulting with their physicians. In addition, some physicians may be unwilling to prescribe products listed on the Drug Watch website because of malpractice concerns. Patients may be switched to alternative therapies not listed on the Drug Watch page that have more common or more serious risks than those potential risks identified on the Drug Watch page.

This outcome could have far greater impact on public health than any risk stemming from the unsubstantiated safety signal. Therefore, PhRMA recommends that any risk communication program FDA adopts include procedures to ensure that information is published only when the potential benefits outweigh the risks, *i.e.*, after the Agency has conducted an evaluation sufficient to allow it to make a determination regarding association or causation.

Even then, the Agency should stress on the Drug Watch website 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 ensure that patients do not unilaterally stop taking safe and effective medicines based solely upon information posted on the Drug Watch website.

In addition, the Agency 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 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 healthcare providers to make informed decisions concerning treatment.

Finally, FDA should conduct consumer research using a mock up of the Drug Watch web page to assess the public health impact of the information posted on the website. A common element in sponsor risk management plans is an obligation to measure the impact and effectiveness of risk communications in the target audience. Here, where the stakes may be higher and the target audience broader, the Agency should likewise implement a plan to analyze the effects of this information on patients and healthcare practitioners. The Agency has often relied upon this type of research in situations where it is recognized that consumer comprehension is critical.¹ Ideally, this should be done as part of a limited pilot program on a select number of drug products before it is broadly implemented.²

C. Drug Product Labeling Should Be the Primary Means of Communicating Safety Information

The Federal Food, Drug and Cosmetic Act 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. The FDA's Drug Watch website should not undermine the role of labeling as the most important source of valid safety information.

Many provisions of the Draft Guidance are consistent with this principle. For example, PhRMA supports FDA's proposal to publish new safety information about an "important risk minimization procedure" put into place by the drug sponsor, or about certain adverse reactions in a specific patient population that FDA has concluded are causally associated with a particular drug product. This information is critical for the safe use of the product and thus either would be reflected in the approved labeling via a supplemental application or would already be consistent with that labeling. PhRMA supports use of the Drug Watch website to publicize this type of important safety information more quickly and more broadly than might be possible with a labeling change.

Other provisions of the Draft Guidance, however, if implemented, would undermine the primacy and usefulness of labeling. In particular, FDA states that it will post "emerging safety information before [FDA has] fully determined its significance or taken final regulatory action." *See* Draft Guidance, Section II., p. 2, lines 64-68. 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. PhRMA submits that revisions to labeling based upon review of data and information submitted in accordance with FDA's regulations provide the appropriate

¹ *E.g.*, in connection with development of Drug Facts labeling.

² In addition to the potential impact on public health, PhRMA also is concerned that posting preliminary information on the Drug Watch website may have an unintended negative effect on the ability of FDA and the sponsor to further investigate the potential safety signal. Publicity surrounding the event could hamper enrollment into prospective epidemiologic and clinical studies. Additionally, spontaneous reporting will inevitably be stimulated by the Drug Watch posting and subsequent media attention, which could result in a "self-fulfilling prophecy" in terms of signal confirmation.

and statutorily mandated vehicle for FDA to ensure that patients and healthcare practitioners have access to current and scientifically valid risk/benefit information. The Drug Watch program, which circumvents this established communication mechanism, would only serve to undercut the reliability of labeling and introduce confusion into the healthcare and patient communities.

Although Drug Watch postings are intended to be a “heads up” to health care professionals, in today’s litigious medical environment it is almost certain that Drug Watch warnings will be used by plaintiff’s attorneys as “proof” of material safety risks, and that courts will allow the warnings as evidence of causation. For example, a recent FDA public health advisory for pimecrolimus and tacrolimus is reportedly a model for future Drug Watch updates. Despite the preliminary nature of the potential cancer risk described in the notification, several plaintiffs’ attorneys have established web sites for patient recruitment, citing the advisory as proof of a causal relationship. Juries 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 unvalidated safety signals, an outcome that is not necessarily in the best interest of patients. It is also possible that some sponsors, in defense of possible 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.

This 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 has proposed reorganizing the approved physician labeling for drug products to include a “Highlights” section identifying the most important safety and effectiveness information. *See* 65 Federal Register 81082 (Dec. 22, 2000). Likewise, FDA has suggested in a draft guidance document that the “brief summary” for direct-to-consumer print advertisements should include only the most important risk information and omit less important risk information. *Draft Guidance on Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements*, Docket No. 2004D-0042. 69 Federal Register 6308 (Feb. 10, 2004). According to FDA, “exhaustive lists of minor risks distract from and make it difficult to comprehend and retain information on the more important risks.” *Draft Brief Summary Guidance* at 2. Yet FDA’s 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 that it intends to use the Drug Watch website to disseminate “important” emerging safety information. 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, *it should be in the labeling*. The goal of the Drug Watch website, therefore, should be to disseminate safety information that is robust enough to be included in the approved labeling in a more widespread and timely manner than could be achieved with a typical labeling revision.

PhRMA and its member companies are committed to 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 the approved labeling. 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. FDA and companies historically have worked well together to ensure that reliable new safety information is provided to healthcare professionals in a timely manner.

PhRMA would like to explore with the Agency the possibility of using the Drug Watch website as part of an accelerated label revision process. In particular, where 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, but if a label change is not finalized at the end of this timeline, FDA would be free to use the Drug Watch website 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 (a) such information is robust, valid and useful; (b) sponsors have a meaningful opportunity for input; and (c) the approved labeling remains the primary means for disseminating safety information. PhRMA would be pleased to discuss this concept further with FDA and other interested stakeholders.

D. There Should Be An Ongoing Dialogue Between FDA and the Sponsor Regarding Safety-Related Information And Its Publication

FDA's Draft Guidance does not make any provision for input from sponsors and instead indicates that FDA will "notify" the sponsor "shortly before" information is posted on the Drug Watch website. *See* Draft Guidance, Section III.D., p. 6, lines 261-18. PhRMA believes it is essential for FDA to consult with sponsors on all emerging safety issues.

FDA and the drug sponsor each have relevant scientific data and information on individual drugs and each have a responsibility to assure that relevant, scientifically valid and useful information is disclosed to healthcare 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 such things 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 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, it is highly likely that regulatory authorities, healthcare 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. PhRMA is concerned by reports that sponsors have not been properly notified prior to recent postings of emerging safety information by FDA.

Another aspect of the notification process that concerns us involves Drug Watch postings for potential class effects, particularly when the adverse event has not been reported with the sponsor's product, although it is a member of the class. An example of such a situation occurred recently when the Agency decided to require black box warnings for all non-steroidal anti-inflammatory agents (NSAIDs). Sponsors of most NSAIDs were unaware that cardiovascular and dermatologic reactions were "emerging safety issues" for their products, and most were put in the awkward position of explaining the new warnings and their lack of supporting evidence to healthcare providers and patients. The Agency should provide sufficient information and documentation to sponsors of all products in the affected class so that they can adequately explain the situation to their customers, as well as to regulatory authorities in other countries where they may market the product.

On the other side of the class effect issue is the concern that in their haste to post information on the Drug Watch web site, FDA may inappropriately single out a particular name brand product, when the issue may actually involve an entire class of drug products (and certainly any generic versions of the branded product).

This lack of an opportunity for constructive input prior to publication is compounded by the chilling effect on constitutionally protected speech of FDA's warning that "[r]epresentations made to minimize the effect of emerging risk information on the site may also be considered false and misleading." *See* Draft Guidance, Section III.E., page 7, lines 242-43. 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. But if that information is by definition too preliminary to support a labeling change or other more formal communication, how can FDA justify a finding that publication of the information is at the same time too urgent to allow a reasonable opportunity for consultation 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. PhRMA recommends that any risk communication adopted by the Agency 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 emerging safety information should be conveyed.

E. FDA Should Not Publish Information That Requires A Disclaimer Stating That The Significance of the Published Information Is Not Known

The Draft Guidance indicates that when FDA publishes information that is still under evaluation, a disclaimer will accompany the information. The Agency does not commit to specific disclaimer language, but offers the following example of a disclaimer 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 web page when additional information or analyses become available.

See Draft Guidance, Section III.A., p. 3, lines 120-24. The Draft Guidance does not address where or how prominently the disclaimer language would appear.

As discussed above, PhRMA does not believe that FDA should disseminate the type of preliminary information that would require the above disclaimer (or similar disclaimers). If a disclaimer of this sort is required, the information by definition is of too preliminary and questionable a nature 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, the Agency should simply refrain from disseminating such information until a disclaimer is no longer required.

III. The Dissemination of Preliminary Safety Information of Unknown Significance Is Inconsistent With Federal Law

Although PhRMA fully endorses many aspects of the proposed Drug Watch program, PhRMA does not support those provisions that would result in the premature disclosure of preliminary information of unknown significance (*i.e.*, information that requires a disclaimer). Disclosing such information on an official Drug Watch website not only constitutes bad public policy (as discussed above) but also may be outside of the scope of FDA's authority.

A. Premature Publication of Preliminary Safety Information is Prohibited by the Data Quality Act

PhRMA believes that the Drug Watch program fails to meet the standards set forth in the Federal Data Quality Act. *See* Section 515 of the Treasury and General Government

Appropriations Act of 2001, Public Law 106-544, H.R. 5658 (the “Act”). The Act establishes 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 that they disseminate. To implement the Act, the Office of Management and Budget issued policy and procedural guidance applicable to all agencies covered by the Act. In furtherance of the Act and the OMB Guidelines the Department of Health and Human Services also adopted individual guidelines, which contain a specific section applicable to the FDA.³ PhRMA believes that some of the information FDA intends to post on the Drug Watch website lacks a critical feature required under both the OMB Guidelines and the HHS Guidelines for all information disseminated: utility.

As discussed in Section II of these comments, FDA’s description of the Drug Watch program raises serious doubts about the usefulness of the information that will be published. Despite FDA’s liberal use of caveats, numerous statements in FDA’s Questions & Answers, for example, raise significant issues regarding the usefulness of the information that will be disseminated under the program. *E.g.*, Questions & Answers (Qs & As), *Proposed Drug Watch Program*, A.1 (“The Drug Watch Web page is a new communication channel FDA is proposing to communicate the most up-to-date information possible on emerging safety issues to the public, *even before FDA fully determines the significance of that information or decides whether a regulatory action is appropriate.*” (emphasis added)). Thus, the program will result in the publication of information of limited or no utility, in direct contravention of HHS’s own data quality guidelines applicable to the FDA: “[w]e only disseminate information that we believe will be useful to the public or a segment of the public.” HHS Guidelines, Part II, § F.V.A.⁴ Notably, both the OMB and HHS Guidelines provide for the review of information to ensure quality *before* dissemination by the agency. HHS Guidelines, Part I, § D.4.e., Part II, § F.V.; OMB Guidelines § III.2.

As repositories for relevant scientific data and information, FDA and the drug sponsor each have a responsibility under the Federal Food, Drug, and Cosmetic Act (FDCA) to assure that relevant, scientifically valid and useful information is disclosed to healthcare practitioners and made available to consumers. PhRMA believes, and the Data Quality Act confirms, that the public is not served by posting information that is so preliminary and vague as to preclude determinations of its clinical or regulatory significance.

³ See OMB Notice: *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies*, 67 Fed. Reg. 8,451 (Feb. 22, 2002); HHS Notice: *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by HHS Agencies*, availability announced at, 67 Fed. Reg. 61,343 (Sept. 30, 2002), and currently available at, <http://aspe.hhs.gov/infoquality/Guidelines/index.shtml>. For clarity, these guidelines will be referred to as the “OMB Guidelines” and the “HHS Guidelines,” respectively.

⁴ 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, §§ III.1, III.2, V.2.

It is clear that publication of preliminary information of unknown meaning or significance fails to meet the basic standard of utility required for all data published by agencies. Publication of this type of information is also inconsistent with the more stringent standards applicable to “influential information.” The HHS Guidelines make clear, as do those published by OMB, that “influential information” is to be subject to “special quality standards.” “Influential” means that “the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions.”⁵ HHS Guidelines, Part II, § F.VII.A.; OMB Guidelines, § V.9. Such influential information “must meet high standards of transparency of the data and methods used to facilitate the reproducibility of such information by third parties.” HHS Guidelines, Part II § F.VII.B. The HHS Guidelines also provide that the “influential, scientific, financial and statistical information that FDA disseminates will meet the high standards in the OMB Guidelines for such information.” *Id.*

Significantly, the HHS Guidelines require “clarity” of the disseminated influential information. Clarity “includes ensuring the information disseminated is clear and understandable.” HHS Guidelines, Part II, § F.VII.B. When disseminating information about risk, the “agency shall ensure that the presentation of information about risk effects is comprehensive, informative, and understandable.”⁶ In the context of a complicated causal or risk assessment of emerging information that is at such a preliminary stage that FDA itself cannot make even a tentative conclusion on causation or offer any guidance to healthcare practitioners or patients, PhRMA believes the requisite clarity and comprehensiveness are simply unattainable.

As the HHS Guidelines explain:

The OMB Guidelines provide that in addition to the ordinary standards for utility, objectivity, and integrity that apply to dissemination of information, special considerations must be taken into account in certain risk assessments, *i.e.*, those that provide the basis for the dissemination of influential information. . . . ‘With regard to analysis of risks to human health, safety, and the environment maintained or disseminated by the agencies, agencies shall either adopt or adapt the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996 (SDWA) (42 U.S.C. 300g-1(b)(3)(A) and (B)). . . .’

⁵ HHS further defines “influential information” in the context of the FDA as “disseminated information that results from or is used in support of agency actions that are expected to have an annual effect on the economy of \$100 million or more or will adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local or tribal governments or communities.” HHS Guidelines, Part II § F.VII.A. Regardless of whether publication on the Drug Watch website rises to the economic level ostensibly required under the HHS Guidelines, because of the potentially serious adverse effects on public health and safety, the information qualifies as influential and, accordingly, the strictest of standards apply.

⁶ HHS Guidelines, Part II § F.VII.C. (describing the data quality principles incorporated into the Safe Drinking Water Act, which are an integral part of the OMB Guidelines and HHS Guidelines).

To the degree that the agency action is based on science, the agency shall use . . . the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices [and] data collected by accepted methods (if reliability of the method and the nature of the decision justify use of the data).

HHS Guidelines, Part II, § F.VII.C. Yet those controls and principles do not appear present in the proposed Drug Watch program. There would be no scientific method, much less peer-review.

In publishing its agency-wide guidelines, OMB emphasized the importance of meeting the Data Quality Act standards: “It is crucial that information Federal agencies disseminate meets these guidelines. . . . Given the administrative mechanisms [enabling aggrieved parties to seek correction of information] required by section 515 [of the Data Quality Act] as well as the standards set forth in the Paperwork Reduction Act, it is clear that agencies should not disseminate substantive information that does not meet a basic level of quality.” 67 Fed. Reg. 8,451, 8,452. OMB also cautioned that the internet raises unique concerns, due to both the ease of publishing information on the internet and the reach of that form of communication:

The fact that 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.

Id.

In developing the Draft Guidance, it appears that FDA failed to take into account the Data Quality Act requirements and the special considerations raised by publication of information of this type on the internet. Insofar as the FDA’s Draft Guidance contemplates publication of information before FDA can assess its meaning, significance, or potential consequences or offer relevant and meaningful guidance to the public, it is inconsistent with the Data Quality Act and impermissible.

B. Some Aspects of The Drug Watch Program Are Inconsistent With The Structure Established By The Federal Food, Drug, and Cosmetic Act for Communicating Risks and Exceed the Limits Placed on FDA’s Authority to Use Publicity

The Drug Watch program, as described in the Draft Guidance, is inconsistent with the structure established by the FDCA for communicating safety-related information, including publicity under Section 705 of the FDCA. 21 U.S.C. § 375.

The 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. 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 incorporated into labeling, both before and after approval of the NDA. 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, 21 U.S.C. § 352(e)(1); (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, 21 U.S.C. § 352(e)(2)); or (c) based upon new information, FDA determines that the labeling of a drug is false or misleading (including by reason of a failure to reveal a material fact), and the labeling is not corrected within a reasonable time after the sponsor receives notice of the matter. 21 U.S.C. § 352(e).

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 approval of the NDA.⁷ 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 proved.” 21 C.F.R. § 201.57(e).⁸

The FDCA also permits the Agency to use publicity to issue a public warning about the safety of a drug product, but only if FDA determines there is an “imminent danger to health, or gross deception of the consumer.” 21 U.S.C. § 375.⁹ PhRMA fully supports the Agency's use of publicity in these types of situations, but notes that the Draft Guidance expressly addresses situations that do not present an imminent danger to health or gross deception of the consumer. Instead, the FDA proposes to publish emerging information about potential side effects or risks that may or may not ultimately be determined to be accurate.¹⁰

⁷ Sponsors are further motivated by public health and sound business practices to promptly institute appropriate labeling changes to help ensure that their products are used safely and the possibility of untoward effects is minimized.

⁸ FDA's regulations also provide a means for the Agency to require inclusion of certain emerging safety information in prescription drug advertising. 21 C.F.R. § 202.1(j).

⁹ There can be no serious dispute that posting product specific information on an official Agency website entitled “Drug Watch,” described as a source of current safety information, constitutes publicity.

¹⁰ Section 705 of the FDCA also specifies that it is not intended to prohibit FDA from “collecting, reporting, and illustrating the results of [its] investigations.” Even if FDA's evaluation of safety information could be considered an “investigation,” it is clear that the guidance contemplates publication *before* there are “results” of any investigation or evaluation, and is thus not authorized by this clause of Section 705. *See, e.g.*, Draft Guidance, Section III.A., p. 4, lines 136-37 (“By definition, however, the information posted on the Drug Watch is information about which FDA has made no final regulatory judgment”).

Although the Draft Guidance does not include a discussion of FDA's authority, the guidance does state that most information that will be published on the Drug Watch website is made available to the public in response to Freedom of Information Act requests. PhRMA agrees that in certain cases, some of the data that FDA is evaluating may be releasable under the FOIA (*e.g.*, post-marketing adverse experience reports, after appropriate redaction). However, even if limited to data that are otherwise releasable, the posting of these data on a Drug Watch website clearly attaches a significance to the data that is not present when data are merely released according to the FOIA. Therefore, FDA's authority under the FOIA does not support the disclosure of data under the circumstances proposed in the Draft Guidance.¹¹

Moreover, the Draft Guidance contemplates posting information about drug safety that would need to be specifically developed for the Drug Watch website. Clearly, such statements would not otherwise be created in the early stages of the Agency's evaluation of a potential safety issue, and thus describing those statements as normally released in response to a FOIA request is inaccurate. It is the publication of the data or statement about drug safety on the Drug Watch page – not the routine release of data consistent with the FOIA – that constitutes impermissible publicity under Section 705 of the Act.

C. A Program Such as Drug Watch Must Be Adopted Through Notice and Comment Rulemaking under the Administrative Procedure Act

Even if the FDA had authority to disseminate preliminary safety information through the Drug Watch program, it must, at a minimum, implement that program pursuant to notice and comment rulemaking.

Section 505 of the Act and FDA's regulations, adopted through notice and comment rulemaking, establish a process through which safety issues are evaluated in consultation with the applicant, in the context of an NDA. If FDA determines that labeling must be revised to address a new safety issue, FDA must provide the applicant notice of the labeling deficiency, and only if the applicant refuses to revise the labeling after a reasonable period of time may FDA take action with withdraw approval of the application. 21 U.S.C. § 505(e); 21 C.F.R. § 314.150(b)(3).

The Drug Watch program, in essence, abandons this established process in favor of one in which FDA will, in effect, unilaterally determine whether labeling provides adequate information for safe use of the drug by effectively amending the conditions of use through the posting of information on the Drug Watch website. This is so even though the information posted would not, at the time of posting, justify a labeling revision under existing regulatory rules and procedures.

¹¹ The reference in the Draft Guidance to the FOIA as authority for Drug Watch postings raises the additional question of FDA's lack of authority to post preliminary information of undetermined scientific or regulatory significance that is not otherwise releasable under the FOIA.

The purported “guidance” in reality provides no guidance to industry or to FDA employees, but rather, constitutes a significant change in existing regulatory procedures and rules for addressing emerging safety information. Agency action that effectively amends a previously adopted regulation, or the Agency’s interpretation of a previously adopted regulation, requires formal rulemaking procedures in accordance with the Administrative Procedure Act, 5 U.S.C. § 553.¹² Accordingly, PhRMA believes it is impermissible for the Agency to attempt to adopt the Drug Watch program through publication of a guidance document.

Moreover, PhRMA believes that the Drug Watch program, because it constitutes such a dramatic change in FDA’s approach to risk communication, would benefit from a more robust and formalized public review process than that afforded by development of a Guidance Document. As a matter of sound regulatory policy, the Agency should seek to implement the Drug Watch program through notice-and-comment rulemaking.

IV. If FDA Decides To Disseminate Preliminary Safety Information On The Drug Watch Website, It Should Revise The Existing Draft Guidance To Mitigate Public Health Concerns

As discussed above, PhRMA fully supports most aspects of the proposed Drug Watch program but opposes those provisions that seek to disseminate preliminary safety information of unknown significance or utility, especially without sponsor involvement and discussion. If FDA nevertheless decides to disseminate this type of preliminary safety information on the Drug Watch website, the Agency should consider the following issues to mitigate the above-described public health concerns.

A. What Information Will Be Posted?

There seems to be an inconsistency between the general inclusion criteria for Drug Watch (emerging safety information) and the examples provided in the section on what will be posted, particularly examples B and C. These examples discuss risks for which a conclusion appears to have been established, rather than emerging safety risks. Specifically, the situations described in lines 96-98, “...risks that FDA believes may be associated with a drug...avoided by appropriate patient selection, monitoring...” and in lines 108-110, “...can cause liver damage. The sponsor has advised prescribers to check a patient’s liver enzymes...” appear to be information that would more appropriately be included in a product’s labeling. Presenting warning information on one single aspect of a drug in isolation may detract from consideration of the full set of warnings and precautions contained in the product’s labeling, as well as consideration of the approved indications, which are important to any individual prescribing

¹² See e.g., *National Family Planning and Reproductive Health Ass’n, Inc. v. Sullivan*, 979 F.2d 227 (D.C. Cir. 1992); *Paralyzed Veterans of America v. D. C. Arena L.P.*, 117 F.3d 579 (D.C. Cir. 1997); *Alaska Professional Hunters Ass’n, Inc. v. FAA*, 177 F.3d 1030 (D.C. Cir. 1999).

decision. It may be useful to provide a link to the approved labeling for the product, so that physicians and other healthcare providers have ready access to the complete prescribing information.

In addition, this section states that Drug Watch will provide information about drugs with *significant* emerging safety issues (line 76), but other parts of the document indicate that the aim of the program is in part to determine if emerging safety issues are, in fact, significant at all. These contradictions generate uncertainty over the range of situations which FDA plans to include on the Drug Watch web page.

In the Introduction section of the draft guidance document, FDA states that they intend to work “as quickly as possible to assess and address the potential safety issues...” (lines 37-38), and lines 130-131 indicate that FDA intends to update information on the Drug Watch frequently. We agree with these statements; however, the guidance document should include more information concerning the nature and frequency of the updating process, such as whether there will be a minimum cycle time for updating, what it will take to resolve an issue, and whether there will be an archive/history that shows the progress of emerging information over time. In addition, we suggest that the Drug Watch posting include information regarding the steps the Agency is taking to assess and address the emerging safety issue, and the estimated timeframe for completion of this assessment.

Because of the nature of some adverse events, and the very low frequency with which they occur, it is possible that an emerging safety issue could be posted to the web page and remain there for months or years without any new information being made available. We suggest that there should be some minimum interval for updating each Drug Watch posting (e.g., 4-6 months), even if the “update” states that no new information has become available. There should also be some criteria for removing a posting after a defined period of time (e.g., 1 year) if no new definitive data become available to resolve the question of causality or risk.

Similar information regarding timeframes and criteria for updating the “emerging safety information” section in the Patient Information Sheets described in footnote 5, as well as some detail regarding how FDA will deal with issues related to version control/outdated information (e.g., if a consumer printed off a Patient Information Sheet last week, how will they know the information has changed this week?; how will patients be informed when “emerging safety information” is removed from the Patient Information sheet because a of a lack of a causal relationship?) is also requested.

B. How Will FDA Decide Which Drugs Will Be Included On the Drug Watch Website?

The criteria for posting information on the Drug Watch web page need to be more explicitly defined. This is particularly important because the information will be posted “before (FDA) has fully determined its significance” (line 65). Given the risk of premature and/or inaccurate posting of information that could lead to confusion among healthcare providers and

patients, it is crucial to have clearly defined parameters for the selection of information to be posted, including meaningful quality control measures.

In lines 153-163, FDA outlines the factors that will be used to decide which drug products and information are posted on the Drug Watch web page. These criteria are quite vague, and raise a number of questions, some of which are listed below. Information to answer these questions should be included in the guidance document.

- It is unclear whether the Drug Watch postings will involve only emerging safety issues that represent serious adverse events (e.g., organ damage, arrhythmias, etc.), or whether any adverse event could be subject to posting.
- The first criteria, “Whether new and emerging safety information could significantly affect prescribing decisions or how patients should be monitored” (lines 153-157), is vague with regard to the strength of the information necessary to make such a determination. How many cases will be needed – one, three, some other number?
- The second criteria (lines 158-161) notes that if measures can be taken as a result of providing information which might prevent or mitigate harm, then that information could be included on the Drug Watch. What about information where there is not an associated measure which might be taken? Is that communicated and if so, how?
- How will it be determined that “an unapproved (off-label) use of the drug appears to pose a significant risk to patients”? (lines 162-163)
- Does FDA have any plans to evaluate the effects of Drug Watch postings on the behavior of healthcare providers or patients/consumers?

Lines 167-168 note that before posting information on the Drug Watch web site, the Agency will conduct a “...preliminary analysis to determine that the new safety information is sufficiently credible...”. Does the Agency plan to publish any information/guidance regarding the thresholds or criteria that might be used in this determination? Examples of such criteria could include pharmacologic plausibility, similar events observed in clinical trials or included in labeling, events observed with other agents in the same class, etc.

Although the draft document goes to great lengths to describe the complete membership of the Drug Safety Oversight Board (DSOB) that will be responsible for determining which products are posted to the Drug Watch web site, according to MaPP 4151-3, a Drug Watch Subcommittee consisting of the DSOB Chair and no more than five additional members will actually make the decisions regarding addition and deletion of information on the web page. The rationale for delegating such important decisions to a small subcommittee is not evident. Since the emerging safety issues to be placed on the Drug Watch web site involve preliminary information that requires further evaluation and verification, there does not appear to be a compelling reason to rush a posting in advance of full consideration by the DSOB. FDA should

consider convening an *ad hoc* meeting of the full DSOB for such decisions if speed is of the essence, rather than having the full Board review decisions of the Subcommittee after the fact. If there is an overriding rationale for having the Subcommittee make decisions regarding Drug Watch postings, rather than the full DSOB, this should be fully described in the guidance document.

C. The Disclaimer Language Should Be Strengthened

As noted above, PhRMA questions whether any disclaimer would ever effectively counteract the message conveyed to the public by the act of posting, *i.e.*, FDA has determined that this drug is unsafe. However, if the Agency implements Drug Watch or a similar program, PhRMA believes it is essential to include the most effective disclaimer language possible.

First, PhRMA urges that the proposed disclaimer language be strengthened. The draft guidance discusses a number of conclusions that *should not* be drawn from FDA's publication: that the product is risky or dangerous, that FDA believes the product is inappropriate for use, that FDA has concluded that there is a causal relationship between the drug product and the risks or adverse events described, or that FDA advises practitioners to discontinue prescribing the product. Similarly, the draft guidance emphasizes that the information posted on Drug Watch is information about which FDA has made no final regulatory judgment. All of these are critical limitations on the information FDA intends to publish, and as such, each should be clearly communicated in any disclaimers used on the web page.

In addition, the disclaimer should seek to emphasize the important role of the healthcare practitioner in evaluating the significance of the new safety information for each individual patient. Thus, 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 ensure that patients do not unilaterally stop taking safe and effective medicines based upon information posted on the Drug Watch website.

In addition, we request that the disclaimer specifically state that the information is not considered sufficient to warrant a change in the product's labeling. The Drug Watch web site should also include an explanation noting that posting of information about a product does not mean that the manufacturer is required to take any specific action related to the posted information.

Finally, FDA must ensure that the disclaimer language is sufficiently prominent and conspicuous to be noticed by users of the website. PhRMA recommends that disclaimer language appear prominently on the Drug Watch home page and also on each screen on which product specific information appears.

D. How Will Drugs Be Removed From The Drug Watch?

The wording in this section regarding criteria for removing a product from the Drug Watch web site is highly subjective, and gives little insight into what the criteria will be, and how they will be applied. It seems that the instances where it can be definitively stated that no new safety concern exists will be extremely rare (e.g., proving there is no causal relationship), thereby making removal of a product from the Drug Watch difficult, if not impossible. We recommend that the Agency develop a more specific decision tree for removal or deactivation of Drug Watch listings, and include it in the guidance document.

As noted in our comments on Section IV.A above, the Agency should also establish criteria for removing a product from the Drug Watch web site if no new definitive data become available after a certain period of time (e.g., one year).

Once information about a sponsor's product has been posted, the Draft Guidance does not include a provision for the sponsor to appeal the decision or to propose alternative wording. A mechanism should be established for the sponsor to request DSOB review, and potentially withdrawal of the posted information, based on criteria demonstrating that the posting was inaccurate or lacked a credible basis.

Documenting resolution of an emerging safety issue is an important aspect of the process that will reassure the public that issues have not just disappeared, thereby instilling greater confidence in the program. Therefore, it is important that when a product is removed from the Drug Watch, it be done in a timely manner, and the rationale for removal and information upon which the decision to remove it is made available on the web site, with the same level of highlighting and publicity that the original posting received. This "exonerating information" should remain on the web site for a specified period of time. We also recommend that the Agency develop and maintain a permanent on-line reference for each issue that is posted to the Drug Watch, including how it was evaluated, and its resolution.

E. FDA Should Consider The International Effect of Drug Watch Communications

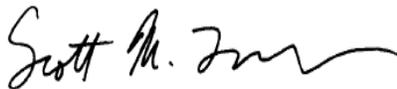
The Agency needs to consider the global impact of FDA public statements posted on their website, which are rapidly cascaded around the globe to health authorities and the media. FDA should take measures to communicate the objectives and procedures for the Drug Watch program to international health authorities. The Agency is in many ways the *de facto* regulator for much of the world. Publicizing unvalidated safety signals is a new concept that, to our knowledge, has not been attempted outside the United States, and its acceptance and interpretation will vary widely in other cultures. We believe the Agency should work closely with other health authorities so they can prepare themselves to handle local public responses to FDA Drug Watch postings.

V. Conclusion

In summary, PhRMA supports many aspects of the proposed Drug Watch program but opposes those provisions that seek to disseminate preliminary information of unknown significance or utility, especially without sponsor involvement and discussion. Such information is not validated, not useful for guiding rational prescribing decisions, and not likely to accomplish anything other than confusion among physicians and the public and creation of irrational fears about the safety of drugs on the list, to the detriment of 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.

PhRMA believes that 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 instead of undercutting it. PhRMA also believes the Drug Watch website may be useful as part of an accelerated labeling revision process in certain circumstances and would be happy to discuss this concept further with the Agency.

Sincerely,



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