Consumer Healthcare
Products Association

August 8, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
*http://www.fda.gov/dockets/ecomments*

Re: Docket No. 2005D-0062
Draft Guidance for Industry on the Food and Drug Administration's "Drug Watch" for Emerging Drug Safety Information (May 2005)
70 *Federal Register* 24606 (May 10, 2005) (Notice of availability)

Dear Sir or Madam:

In the May 10, 2005 *Federal Register*,[1] the U.S. Food and Drug Administration ("FDA") announced the availability of and invited comments on the above-referenced draft guidance. The guidance explains how FDA intends to develop and disseminate important emerging drug safety information concerning marketed drug products to healthcare professionals and patients in an easily accessible on-line format entitled "Drug Watch". Unlike previous forums, the information will be disseminated before the Agency has fully determined the significance of the information, causal or otherwise, or taken final regulatory action.

Drug Watch applies to both prescription and nonprescription or over-the-counter ("OTC") drug products as well as therapeutic biological products regulated by the Center for Drug Evaluation and Research ("CDER").[2] Presumably, OTC drug products marketed in compliance with an OTC drug monograph as well as those marketed under the authority of an approved product-specific new drug application ("NDA") or an abbreviated NDA will be within the program's coverage. All of the products appearing on Drug Watch must present "significant emerging safety issues."

---

[1] "Draft Guidance for Industry on the Food and Drug Administration's 'Drug Watch' for Emerging Drug Safety Information; Availability," 70 *Fed. Reg.* 24606 (May 10, 2005) (Notice).

[2] Draft guidance at 1, n.2; *see also* Questions and Answers ("Q&A") at 2 (Q5) (available at *http://www.fda.gov/cder/guidance/6657qs&asext5-2.pdf*).

900 19th Street, NW
Washington, DC 20006
Tel: 202-429-9260
Fax: 202-223-6835
www.chpa-info.org

A key point emphasized by FDA is that drugs listed on Drug Watch do not present "a real [or validated] safety concern."[3] Accordingly, listed drugs may continue to be used without interruption, although FDA cautions that "healthcare professionals and patients can consider the information when making decisions about a patient's medical treatment."[4] On a related note, even if the information posted by FDA on Drug Watch conflicts with a product's approved labeling, this does not mean that a labeling or similar change will be required in order for the manufacturer to continue marketing the product. Rather, a listing simply represents an on-line codification of certain drugs – temporarily, in some cases – reflecting FDA's "preliminary analysis" of available data, such as newly observed, serious adverse events concerning the drug, based upon listing criteria established by FDA.[5]

The Consumer Healthcare Products Association ("CHPA"), founded in 1881, is the national trade association representing manufacturers and distributors of OTC drugs and dietary supplements in the United States. CHPA members account for over ninety (90) percent of the domestic retail sales of OTC drugs. Moreover, CHPA has been a major participant in every aspect of OTC drug regulation, including the OTC Drug Review, switch procedures, manufacturing controls, and advisory committee activities.

As mentioned above, because FDA intends Drug Watch to apply to OTC drugs, Drug Watch has the potential to affect a substantial proportion of the CHPA membership. CHPA has supported and continues to support the timely provision of complete and accurate product information to healthcare professionals and patients in an easily accessible format, and commends the Agency for considering new approaches to disseminating emerging drug safety-related data. But given the preliminary nature of the information to be disseminated by FDA on Drug Watch, the information falls short of the guidelines promulgated by the U.S. Department of Health and Human Services ("HHS") and FDA for ensuring and maximizing the quality, objectivity, utility, and integrity of information disseminated to the public.[6]

---

[3] Draft guidance at 1.

[4] Draft guidance at 4.

[5] The criteria are set forth in the draft guidance. They are: 1) Whether new and emerging safety information could significantly affect prescribing decisions or how patients should be monitored (new risks); 2) whether measures can be taken as a result of providing information that could help to prevent or mitigate harm (new information on known risks); and 3) whether an unapproved or off-label use of the drug appears to pose a significant risk to patients (risks associated with off-label uses). FDA also states as a catch-all criterion that it "may also consider other factors as appropriate." Draft guidance at 4-5.

[6] FDA: "Guidelines for Ensuring the Quality of Information Disseminated to the Public" (available at *http://aspe.hhs.gov/infoquality/Guidelines/fda.shtml*) ("FDA Data Quality Guidelines"); and HHS: "HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public" (available at *http://www.hhs.gov/infoquality/part1.html*). The relevant statutory

Moreover, Drug Watch: 1) risks confusing and alarming the public by disseminating safety information about drugs that may change, be incomplete, inaccurate, or never shown to be valid;[7] 2) is in need of clearly defined listing criteria appropriate for OTC drugs; 3) erects an overly stringent standard of removal while also omitting a timeline and delineated process for manufacturer input or discussion or requests for further review; 4) lacks vital OTC drug-specific information, in that the guidance does not provide examples of OTC drug postings and does not address the impact a listing could have on the ability of a consumer to self-select – a key consideration that fundamentally distinguishes OTC drugs from prescription drugs – when the Drug Watch information is at odds with the approved product labeling; 5) proposes a disclaimer that is not a disclaimer at all; and 6) does not do enough to protect the rights of manufacturers or sponsors prior to a drug's listing.

For these reasons, CHPA urges FDA to revise Drug Watch in accordance with the recommendations set forth below before the system is enacted.

1. **Disseminating safety information about drugs that must "warrant further consideration to determine whether an actual safety problem exists" will confuse and alarm the public**

As mentioned above, drugs listed on Drug Watch do not present "a real [or validated] safety concern." They do not present a real or validated safety concern because FDA has only undertaken a preliminary analysis of the data with respect to the drug. Thus, the significance or merit of the data, causal or otherwise, has not been confirmed.

CHPA is concerned about the early release of this information before it has been fully vetted by the Agency or the product manufacturer.[8] Disseminating drug safety information that must "warrant further consideration to determine whether an actual safety problem exists" will confuse and alarm the public. It will confuse and alarm the public because the information may change, be incomplete, inaccurate, or never shown to be valid. Also, as explained below, where that information conflicts with the approved product labeling, the OTC consumer who acts without the professional supervision of a licensed practitioner or learned intermediary, may forego treatment altogether out of unjustified concern about the

---

provision is popularly known as the "Data Quality Act" (section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554; H.R. 5658)).

[7] Draft guidance at 5 (all of the information to be posted by FDA on Drug Watch must "warrant further consideration to determine whether an actual safety problem exists").

[8] In Section 6 of these comments, we call attention to concerns about the Agency's determination to minimize the role of the manufacturer or sponsor prior to a drug's listing on Drug Watch.

drug.[9] Drug Facts would be rendered essentially useless because of questions consumers would raise about its legitimacy due to inconsistencies with information posted on Drug Watch.

As a statutory matter, information disseminated by FDA must conform to baseline requirements related to quality, objectivity, utility, and integrity, which the Agency has articulated in the FDA Data Quality Guidelines.[10] The information to be posted by FDA on Drug Watch does not conform to these standards because it has not been subjected to "a rigorous review and clearance evaluation" and lacks the requisite level of utility.[11] Moreover, the lack of manufacturer involvement prior to a drug's listing undercuts the Agency's key goal of transparency during this process.[12] Finally, not one of the eight (8) specific exceptions carved out by FDA in the FDA Data Quality Guidelines applies to the type of information to be posted by FDA on Drug Watch.[13]

CHPA urges FDA to disseminate information on Drug Watch only after it has undergone a rigorous review and clearance evaluation in consultation and discussion with the product manufacturer or sponsor, and the merit of the data, including its causal significance, has been established. On a related note, the public summaries provided by the Drug Safety Oversight Board must be detailed and contain specific information from the meeting in order to be useful.[14]

**2. Drug Watch is in need of clearly defined listing criteria appropriate for OTC drugs**

Before a drug may be listed on Drug Watch, it must undergo a preliminary analysis. This analysis will be conducted by the Drug Safety Oversight Board and CDER Director.

---

9 *See* Section 4 of these comments.

10 *Supra* n.6.

11 FDA Data Quality Guidelines at 8 (of 27) (Section V) and 9-10 (of 27) (Section V.A).

12 *See also* Section 6 of these comments.

13 FDA Data Quality Guidelines at 3 (of 27) (Section II). The eight exceptions are: documents relating to internal FDA procedures; internal government correspondence; correspondence with individuals that is not normally made public; press releases; archival records; distributions intended to be limited to subpoenas or adjudicative documents; certain scientific publications; and responses to FOIA requests.

14 CHPA raises this concern due to the extreme brevity of the June 17 and July 27, 2005 public summaries.

Specifically, the Drug Safety Oversight Board and CDER Director will adjudicate which information to include on Drug Watch based upon listing criteria established by FDA.[15]

The listing criteria established by FDA in the draft guidance are:

- Whether new and emerging safety information could significantly affect prescribing decisions or how patients should be monitored (e.g., a drug that has been identified with a possible association with renal failure should not be prescribed to patients with renal disease; a new possible drug-drug interaction has been identified and needs to be considered in prescribing);
- Whether measures can be taken as a result of providing information that could help to prevent or mitigate harm (e.g., limit prescribing to patients most likely to benefit from the drug, conduct special monitoring of patients on the drug, be alert for signs of serious adverse reactions);
- Whether an unapproved (off-label) use of the drug appears to pose a significant risk to patients; and
- Other factors as appropriate.[16]

For OTC drugs, however, these criteria are ill-suited because they raise considerations pertinent to prescription drugs only. As a result, how or on what basis an OTC drug will be added to Drug Watch is largely unknown and therefore prompts concerns of arbitrariness. In addition, the draft guidance does not clearly define numerous concepts and terms of art, such as:

What constitutes a "preliminary analysis"?
What qualifies as a "significant" emerging safety issue or risk?
What is a "serious" new side effect?[17]
Are all new side effects also "unexpected"?[18]
What does FDA mean when it says that it "may also consider other factors as appropriate"?

---

[15] *Supra* n.5; *see also* MAPP 4151-3: Drug Safety Oversight Board (CDER).

[16] Draft guidance at 5 (emphases supplied).

[17] The term "serious" must be defined by FDA in accordance with existing regulatory standards. *See* 21 C.F.R. § 314.80(a) (definition of "serious adverse drug experience").

[18] *See* 21 C.F.R. § 314.80(a) (definition of "unexpected adverse drug experience").

Who is the "relevant sponsor," especially for OTC products subject to the OTC Drug Review (*i.e.*, monograph OTCs)?

Under what circumstances will an entire "class" of products be listed?

Must the CDER Director only consider the recommendation(s) of the Drug Safety Oversight Board (*i.e.*, no additional outside evidence)?

Etc.

In sum, clearly defined listing criteria appropriate for OTC drugs are needed.

**3. Drug Watch erects an overly stringent standard of removal while also omitting a timeline and delineated process for manufacturer input or discussion or requests for further review**

As mentioned above, information will be posted on Drug Watch if FDA finds any "early safety signals" about a drug. However, the only mechanism to remove the drug from Drug Watch is if the manufacturer is able to prove, and FDA determines the definitive safety of the drug.

> As safety issues are resolved, FDA intends to promptly remove drugs from the Drug Watch. For example, a drug may be removed from the Drug Watch when its labeling has been revised to address the safety concerns, when FDA has taken other steps to adequately communicate information to healthcare professionals and patients, or when FDA has determined that, despite the initial signals, there is no new safety concern.[19]

Besides the obvious lopsidedness of this approach, this 'easy to get on, hard to get off' framework unfairly burdens manufacturers because once information about a drug is posted on Drug Watch, the damage is done. This is because the OTC consumer, who generally acts without the professional supervision of a practitioner licensed by law, will view the product with confusion and alarm, and may avoid taking the OTC product altogether as a result of the listing.

In addition, manufacturers are left guessing as to what FDA means by "[a]s safety issues are resolved" or "when FDA has taken other steps to adequately communicate information to healthcare professionals and patients" or "when FDA has determined that…there is no new safety concern." The criteria for de-listing must be thoroughly articulated by FDA.

---

[19] Draft guidance at 6.

FDA has indicated that it will "work as quickly as possible to assess and address the potential safety issues identified on Drug Watch."[20] But neither the draft guidance nor the Q&A document proposes a specific timeline or process for doing so. The only guidance provided by FDA in this regard is that the Board will meet "on an 'as needed' basis."[21] A detailed plan of review and timeline are needed from the Agency.

CHPA agrees that stakeholder input must be considered after information is posted to the web page, and that FDA must carefully review any comments it receives once a drug is listed on Drug Watch to see if, among other things, there are any factual errors that need correcting.[22] Also, FDA must consider input from manufacturers and others outside the Agency before taking any regulatory action on products listed on Drug Watch.[23] Formalization of these procedures for both NDA'd and monograph OTC drugs is also needed.

On a related note, although CHPA agrees that Drug Watch postings must be changed or removed once the Agency has resolved the alleged safety issue or taken final regulatory action, FDA should also correspondingly change or remove the related *Patient Information Sheet(s)* and *Healthcare Professional Information Sheet(s)*.[24] Changing or removing the related information sheet(s) will avoid further confusion and alarm about the drug.

**4. Drug Watch lacks vital OTC drug-specific information, in that it does not provide examples of OTC drug postings and does not address the impact a listing could have on the ability of a consumer to self-select – a key consideration that fundamentally distinguishes OTC drugs from prescription drugs – when the Drug Watch information is at odds with the approved product labeling**

As mentioned above, FDA intends Drug Watch to apply to OTC drugs.[25] However, the draft guidance only provides examples of prescription drug postings; none are given of

---

[20] Draft guidance at 1; *see also* Q&A at 1 (Q3).

[21] Q&A at 4 (Q3).

[22] "FDA 'Drug Watch' Website: Manufacturers Will Not Have Pre-Posting Input," *The Pink Sheet* at 4 (May 30, 2005) (attribution to and quotation of Office of New Drugs (OND) Director John Jenkins).

[23] *Id.* (attribution to CDER Acting Director Steven Galson).

[24] "FDA 'Drug Watch' Website: Manufacturers Will Not Have Pre-Posting Input" in *The Pink Sheet* at 5 (May 30, 2005) (a contrary position is voiced by OND Director Jenkins, in that "there might still be the patient information sheet, the physician information sheet on the website").

[25] *Supra* n.2.

OTC drugs, and there is no discussion of OTC drug-specific issues (*e.g.*, self-selection). This asymmetry, as explained below, poses problems for OTC drug manufacturers and consumers on a number of levels.

First, the absence of any OTC drug examples in the guidance constrains the ability of manufacturers to advise the Agency of any potential problems with these listings. Manufacturers of OTC drugs deserve the same opportunity as that being afforded to prescription drug manufacturers in this regard.

Secondly, and more critically, lacking in the guidance is a discussion regarding the impact a listing could have on the ability of consumers to self-select when the Drug Watch information is at odds with the approved product labeling, a possibility confirmed in the draft guidance.[26]

Unlike prescription drugs which may only be obtained by consumers "under the professional supervision of a practitioner licensed by law to administer such [a] drug,"[27] the principal resource for consumers to consult regarding OTC drugs is the OTC label. The OTC label contains critical information that must be followed to ensure that the product is taken in a safe and effective manner.[28] Over the years, CHPA and FDA have collaborated to improve the OTC label, specifically Drug Facts, to make it as easy to read and understand as possible.

If the information posted on Drug Watch conflicts with the OTC labeled information, consumers will be confused, plain and simple. Consumers will be confused because they do not have at their disposal a learned intermediary who is knowledgeable to interpret this information. Merely disclaiming the information on *Patient Information Sheets*[29] will not be

---

[26] Draft guidance at 3 ("relabeling the drug") and 4, n.5 ("[i]nformation from the Drug Watch that is not in the final labeling of the product…"). OND Director Jenkins has also expressed in public statements that "[b]y definition, [the site] is going to include some information that is new and hasn't been fully vetted by the Agency, and therefore hasn't made its way into the approved labeling." "FDA Will Alert Drugmakers Before Placing Products on Drug Watch Website" in FDAnews Drug Daily Bulletin, Vol. 2, No. 108 (June 2, 2005); *see also* "FDA 'Drug Watch' Website: Manufacturers Will Not Have Pre-Posting Input" in *The Pink Sheet* at 5 (May 30, 2005) (quoting OND Director Jenkins).

[27] 21 U.S.C. § 353(b).

[28] The OTC label contains critical information regarding the product's active and inactive ingredients; uses of the product; product warnings; the purpose of the medication; directions pertaining to specific age categories, how to take, how much to take, and how often and how long to take; and other information on how to store the product properly and on certain ingredients (e.g., the amount of calcium, potassium, or sodium the product contains). *See* 21 C.F.R. part 201.

[29] Draft guidance at 4, n.5.

an effective solution to these concerns.[30] Also, the consumer's need for guidance in this situation would far exceed any benefit regularly updated status reports could provide.[31]

Any incongruity between the Drug Watch information and the OTC labeled information will make it impossible for the consumer, even a well-educated one who reads and follows Drug Facts, to make a treatment decision with confidence. Drug Facts would be rendered essentially useless because of questions consumers would raise about its legitimacy. In this instance, the consumer may lose the benefit of the OTC drug by foregoing treatment altogether.

FDA must address any inconsistency between the Drug Watch information and the OTC labeled information explicitly and on a case-by-case basis. Furthermore, it must do so on the Drug Watch web page at the time the information is initially disseminated to healthcare professionals and patients. The Agency must also give clear and specific direction to consumers regarding the continued use of the OTC product in a safe and effective manner (e.g., "Stop use and consult a doctor if the condition persists or gets worse.").

**5. Drug Watch proposes a disclaimer that is not a disclaimer at all in that it does not renounce or repudiate that FDA has made a safety finding**

In an effort to inform the public that the safety information on Drug Watch is emerging and requires further evaluation, FDA has proposed the following disclaimer:

> "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."[32]

But the proposed disclaimer is not a disclaimer at all in that it does not renounce or repudiate that FDA has made a safety finding. Instead, it purports to be an affirmative statement concerning an FDA safety finding, albeit a preliminary one. Thus, the proposed disclaimer does not adequately inform healthcare professionals, patients, and (invariably)

---

30 *See* Section 5 of these comments, where we suggest changes to the proposed disclaimer.

31 Draft guidance at 4 ("[W]e also intend to provide information about the status of our analysis…for example, that we have not yet determined whether the reported side effects have been caused by the drug, but we are continuing to analyze the data…").

32 Draft guidance at 3.

plaintiffs' lawyers regarding the true – and extremely limited – meaning of the posted information. For example, it does not communicate that the information posted on Drug Watch is information about which FDA has made no final regulatory judgment or concluded there exists a causal relationship between the drug product and the risks or adverse events described. It also leaves open questions about continued use of the product.

For these reasons, CHPA recommends that FDA utilize a statement drawn from the draft guidance in place of the proposed disclaimer that would address these concerns. The substitute disclaimer is as follows:

> The purpose of the Drug Watch Web page is to communicate significant emerging safety information about specific drug products or classes of drug products. This emerging safety information may relate to new risks, new information on known risks, or risks associated with off-label uses. By definition, however, the information posted on the Drug Watch is information about which FDA has made no final regulatory judgment. Posting information on the Drug Watch Web page does not mean that FDA has concluded there is a causal relationship between the drug product and the risks or adverse events described. Such posting also does not mean FDA is advising practitioners to discontinue prescribing the products that appear on the Drug Watch, or that consumers should stop using the products. Instead, our goal is to make emerging safety information available to the public so that healthcare professionals, patients, and consumers can consider the information when making decisions about medical treatment.[33]

To further underscore the point that "[p]osting information on the Drug Watch Web page does not mean that FDA has concluded there is a causal relationship between the drug product and the risks or adverse events described," CHPA additionally recommends the disclaimer also contain the following statement (or a version thereof), which constitutes an "advisory opinion" that appears in numerous preambles to final OTC Drug Review regulations:[34]

> FDA's decision to act in an instance such as this one need not meet the standard of proof required to prevail in a private tort action (*Glastetter*

---

[33] *See* Draft guidance at 4. The statement in the draft guidance has been modified slightly to address OTC consumer use and treatment decisions.

[34] 21 C.F.R. § 10.85(d)(1).

> v. *Novartis Pharmaceuticals, Corp*., 252 F.3d 986, 991 (8th Cir. 2001)). To mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation.[35]

Without this statement, Drug Watch will likely have the unintended, yet practical effect of prompting plaintiffs' lawyers to file lawsuits against manufacturers of OTC and prescription drug products based upon the Drug Watch listings. The resources necessary to defend against such frivolous allegations would likely be in the millions.

**6. Drug Watch does not do enough to protect the rights of manufacturers or sponsors prior to a drug's listing**

As mentioned above, CHPA supports the timely provision of complete and accurate product information to healthcare professionals and patients in an easily accessible format. CHPA also believes that Drug Watch, when properly formulated, can help achieve this goal in an effective and meaningful way.

However, CHPA is concerned that Drug Watch does not do enough to protect the rights of manufacturers or sponsors prior to a drug's listing. Specifically, although FDA "intends to notify the relevant sponsor that information about its drug will be placed on the Drug Watch shortly before the first instance in which information about that drug is posted on the web site,"[36] the sponsor "will not have a say regarding what drug safety information is posted," nor will the sponsor "have an opportunity to review the documents and provide comment or input before they're posted" or "negotiate the content that will be posted on Drug Watch."[37] The term "shortly before" is not defined by FDA.

FDA should allow affected manufacturers or sponsors the opportunity to review and discuss with the Agency any emerging drug safety information before that information is posted to Drug Watch. This is because the manufacturer or sponsor is often the best resource to evaluate any emerging information about the safety of the drug it makes. As noted by FDA in the draft guidance, "[s]ponsors are the most frequent source of reported information about serious side effects, and FDA regularly discusses emerging risk information with sponsors to

---

35 *E.g.*, "Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use; Final rule," 67 *Fed. Reg.* 72555, 72556 (December 6, 2002).

36 Draft guidance at 6.

37 "FDA 'Drug Watch' Website: Manufacturers Will Not Have Pre-Posting Input" in *The Pink Sheet* at 4 (May 30, 2005) (attribution to and quotation of OND Director Jenkins).

further its evaluation of the information and determine an appropriate course of action."[38] Furthermore, because a drug may remain on the Drug Watch web page for a considerable period of time, and given the concerns mentioned above about confusion and alarm, FDA should exhaust all of the resources it has available before moving forward with a listing.[39]

CHPA urges relevant sponsors be able to attend and participate in meetings with FDA when new drug safety information is being discussed. In addition, the term "shortly before" should be clearly defined by FDA to be equal to or greater than three (3) business days. This would allow affected manufacturers or sponsors time to prepare for the listing and related matters.

**Conclusion**

In closing, CHPA would like to thank FDA for the opportunity to comment on the draft guidance and proposed Drug Watch program. We look forward to working with you in the future on these and other issues important to the OTC drug community. If you have any questions about the enclosed comments, please do not hesitate to contact me at (202) 429-3525 or plarsen@chpa-info.org.

Respectfully submitted,

Paul J. Larsen, Esq.
Assistant General Counsel

cc: Dr. Janet Woodcock
Dr. Steven K. Galson
Dr. Charles J. Ganley
Gerald F. Masoudi, Esq.

---

[38] Draft guidance at 3, n.4.

[39] *See also* 21 U.S.C. § 355(e) (initiation of withdrawal of drug approval requires "due notice and opportunity for hearing").