

DRUG SAFETY OVERSIGHT BOARD

Center for Drug Evaluation and Research

Chair (Non-voting)

- Dr. Douglas Throckmorton, Deputy Director, Center for Drug Evaluation and Research

Executive Secretary

- Dr. Susan Cummins, Executive Director, Drug Safety Oversight Board, Center for Drug Evaluation and Research

Office of New Drugs (OND)/Office of Drug Evaluation (ODE)

Primary Members:

- Dr. John Jenkins, Director, Office of New Drugs
- Dr. Florence Houn, Director, Office of Drug Evaluation III
- Dr. Debra Birnkrant, Director, Division of Anti-Viral Drug Products

Alternate Members:

- Dr. Sandra Kweder, Deputy Director, Office of New Drugs
- Dr. Robert Meyer, Director, Office of Drug Evaluation II

Office of Pharmacoepidemiology and Statistical Science (OPaSS)/Office of Drug Safety (ODS)

Primary Members:

- Dr. Paul Seligman, Director, Office of Pharmacoepidemiology and Statistical Science
- Dr. Anne Trontell, Deputy Director, Office of Drug Safety
- Dr. Gerald Dal Pan, Director, Division of Surveillance, Research and Communication Support

Alternate Members:

- Dr. Mark Avigan, Director, Division of Drug Risk Evaluation
- Dr. Carol Holquist, Director, Division of Medication Errors and Technical Support

Office of Pharmacoepidemiology and Statistical Science (OPaSS)/Office of Biostatistics (OB)

Primary Member:

- Dr. Robert O’Neill, Director, Office of Biostatistics

Alternate Member:

- Dr. Charles Anello, Deputy Director, Office of Biostatistics

Office of Counter Terrorism and Pediatric Drug Development (OCTAP)

Primary Member:

- Dr. Solomon Iyasu, Acting Deputy Director, Division Pediatric Drug Development

Alternate Member:

- Dr. Lewis Schrager, Team Leader, Division of Counter Terrorism

Office of Compliance (OC)

Primary Member:

- Dr. Susan Allen, Associate Director, Scientific and Medical Affairs

Alternate Member:

- David Horowitz, Director, Office of Compliance

Office of Pharmaceutical Science (OPS)

Primary Member:

- Dr. Dena Hixon, Associate Director for Medical Affairs, Office of Generic Drugs

Alternate Member:

- Dr. Lawrence Yu, Director for Science

Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

Primary Member:

- Dr. Lawrence Lesko, Director, Office of Clinical Pharmacology & Biopharmaceutics

Alternate Member:

- Dr. Robert Powell, Senior Pharmacist, Office of Clinical Pharmacology & Biopharmaceutics

Office of Medical Policy

- Dr. Robert Temple, Director, Office of Medical Policy (Non-voting)

Center for Biologic Evaluation and Research

Primary Member:

- Dr. Karen Midthun, Deputy Director, Center for Biologic Evaluation and Research

Alternate Member:

- Dr. Miles Braun, Director, Division of Epidemiology

Center for Devices and Radiological Health

Primary Member:

- Dr. Kimber Richter, Deputy Director for Medical Affairs, Office of Compliance

Alternate Member:

- Dr. Thomas Gross, Division of Postmarket Surveillance

Department of Veterans Affairs

Primary Member:

- Dr. Chester B. Good, Staff Physician, Veterans Administration Pittsburgh Health Care System; Chairman, Medical Advisory Panel for Pharmacy Benefits Management, Department of Veterans Affairs

Alternate Member:

- Dr. Peter Glassman, Staff Physician, Veterans Administration Hospital of Greater Los Angeles and Co-Director, Center for Medication Safety, Department of Veterans Affairs

National Institutes of Health, National Cancer Institute

Primary Member:

- Dr. Anthony Murgo, Acting Chief, Investigational Drug Branch, Associate Chief for Developmental Chemotherapy Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis

Alternate Member:

- Dr. Margaret Mooney, Clinical Investigations Branch ,Cancer Treatment Evaluation Program

Drug Safety Oversight Board Meetings Public Summaries

June 17, 2005 Meeting

The Food and Drug Administration's (FDA) Drug Safety Oversight Board (DSB) held its first meeting on June 17, 2005. The Board met to discuss organizational issues and logistics. The meeting also included an overview of the draft Drug Watch Guidance, the Board policies and procedures and information about routine administrative activities. No product specific issues were discussed.

July 27, 2005 Meeting

The Food and Drug Administration's (FDA) Drug Safety Oversight Board (DSOB or Board) held its second meeting on July 27, 2005, from 11:00 a.m. until 3:00 p.m. The following items were discussed:

- FDA staff briefed the Board about the role of the Office of New Drugs in drug safety, and the safety activities of the Office of Drug Safety.
- FDA staff described for the Board the actions taken since the last Board meeting (June 17, 2005) on significant emerging drug safety issues, in particular the actions on the Fentanyl Transdermal Patch and Palladone (see the recent Public Health Advisories on these drugs at www.fda.gov/cder/drug/default.htm). The Board members then discussed and commented on some of the actions, including issues related to the safe use of opioids in complex drug delivery systems such as extended release products.
- FDA actions on emerging drug safety issues included posting new or updated information for patients and healthcare professionals at www.fda.gov/cder on the following drugs:
- *Updated Healthcare Professional and Patient Information Sheets*
 - Antidepressants – Celexa (citalopram), Cymbalta (duloxetine), Effexor (venlafaxine), Lexapro (escitalopram), (fluvoxamine), Paxil (paroxetine), Prozac (fluoxetine), Remeron (mirtazapine), Serzone (nefazodone), Wellbutrin (bupropion), Zoloft (setraline)
- *New Healthcare Professional and Patient Information Sheets*
 - Erectile Dysfunction Drugs – Cialis (tadalafil), Levitra (vardenafil), and Viagra (sildenafil citrate)
 - Fentanyl Transdermal Patch
 - Iressa (gefitinib)
 - Mifeprex (Mifepristone)
 - Palladone (no patient information sheet because sponsor suspended sales and marketing)

September 8, 2005 Meeting

The Food and Drug Administration's (FDA) Drug Safety Oversight Board (DSOB or Board) held its third meeting on September 8, 2005, from 8:30 a.m. until 4:30 p.m.

The primary focus of the meeting was to start a discussion of the factors to be considered when deciding whether to notify the public about an important emerging drug safety concern. To assist the discussion, FDA staff briefed the Board on recent actions taken on emerging drug safety issues, including Adderall (amphetamine salts), and the Erectile Dysfunction Drugs – Cialis (tadalafil), Levitra (vardenafil), and Viagra (sildenafil citrate). The Board members then discussed and commented on the examples and how one might generalize criteria from them to guide decisions for future emerging safety concerns.

FDA staff also described for the Board the one action taken since the last Board meeting (July 27, 2005) on a significant emerging drug safety issue – the strengthened risk management program, called iPLEDGE, for Accutane (isotretinoin) and generic isotretinoin (see the recent Public Health Advisory on this drug at <http://www.fda.gov/cder/drug/infopage/accutane/default.htm>).

**HEALTHCARE PROFESSIONAL AND PATIENT INFORMATION SHEET
CURRENTLY POSTED ON CDER'S WEBSITE
AS OF AUGUST 24, 2005**

<http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm>

The list below reflects all Healthcare Professional and Patient Information Sheets that have been posted to CDER's website. The drugs that are bolded and are annotated with an asterisk are ones for which CDER requested that the manufacturer make a change to the labeling. The alert section of the sheets should be updated to reflect the labeling change once supplement has been approved by CDER.

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Accutane (isotretinoin)	05/2005	08/2005		No – RMP was already approved.
Adderall (amphetamine)	02/2005			No – FDA still evaluating situation.

Antidepressants

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Celexa (citalopram)	05/2005		07/2005	No – Labeling previously approved.
Cymbalta (duloxetine)	05/2005	06/2005	07/2005	No – Labeling previously approved.
Effexor (venlafaxine)	05/2005		07/2005	No – Labeling previously approved.
Lexapro (escitalopram)	05/2005		07/2005	No – Labeling previously approved.
(fluvoxamine)	05/2005		07/2005	No – Labeling previously approved.
Paxil (paroxetine)	05/2005		07/2005	No – Labeling previously approved.
Prozac (fluoxetine)	05/2005		07/2005	No – Labeling previously approved.
Remeron (mirtazapine)	05/2005		07/2005	No – Labeling previously approved.
Serzone (nefazodone)	05/2005		07/2005	No – Labeling previously approved.
Wellbutrin (bupropion)	05/2005		07/2005	No – Labeling previously approved.
Zoloft (sertraline)	05/2005		07/2005	No – Labeling previously approved.

Atypical Antipsychotics

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
*Abilify (aripiprazole)	04/2005			<i>Yes – Will check with Project Manager.</i>
*Clozaril (clozapine)	04/2005			<i>Yes – Will check with Project Manager.</i>
*Geodon (ziprasidone)	04/2005			<i>Yes – Will check with Project Manager.</i>
*Risperdal (risperidone)	04/2005			<i>Yes – Will check with Project Manager.</i>
*Seroquel (quetiapine)	04/2005			<i>Yes – Will check with Project Manager.</i>
*Symbyax (olanzapine/fluoxetine)	04/2005			<i>Yes – Will check with Project Manager.</i>
*Zyprexa (olanzapine)	04/2005			<i>Yes – Will check with Project Manager.</i>

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Cordarone (amiodarone)	05/2005			No – Warning was provided via sheets.

COX-2 Selective NSAIDs

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Bextra (valdecoxib)	04/2005			No – Sales and marketing have been suspended.
*Celebrex (celecoxib)	04/2005			<i>Yes – Labeling supplement was approved after posting. (Sheets should be updated.)</i>

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Crestor (rosuvastatin)	03/2005			No – Labeling was approved at time of posting.
Duragesic Transdermal Patch (fentanyl)	07/2005			No – Warning was provided via PHA and sheets.

Erectile Dysfunction Drugs

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Cialis (tadalafil)	07/2005			No – Labeling was approved at time of posting.
Levitra (vardenafil)	07/2005			No – Labeling was approved at time of posting.
Viagra (sildenafil citrate)	07/2005			No – Labeling was approved at time of posting.

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Gabitril (tiagabine)	02/2005			No – Labeling was approved at time of posting.

Immunosuppressant Calcineurin Inhibitors

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Elidel (pimecrolimus)	03/2005			No – Warning was provided via PHA and sheets.
Protopic (tacrolimus)	03/2005			No – Warning was provided via PHA and sheets

DRUG NAME	DATE FIRST POSTED	UPDATED	UPDATED	DID FDA REQUEST A LABELING CHANGE THAT WAS NOT APPROVED BEFORE THE POSTING OF THE SHEETS?
Iressa (gefitinib)	06/2005			No – Labeling was approved at time of posting.
Mifeprex (mifepristone)	07/2005			No – Warning was provided via PHA and sheets.
Palladone (hydromorphone)	07/2005			No – Sales and marketing have been suspended.
*Reminyl (galantamine)	03/2005			<i>Yes – Labeling supplement was approved after posting.</i>
Tysabri (natalizumab)	02/2005			No – Sales and marketing have been suspended.

R/D:TMartin:08/24/05

OFFICE OF THE CENTER DIRECTOR

Drug Safety Oversight Board (DSB)

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PURPOSE

This MAPP describes the organizational structure, roles, and responsibilities of the Drug Safety Oversight Board (DSB) in the Center for Drug Evaluation and Research (CDER).

POLICY

The DSB has been established to provide independent oversight and advice to the Center Director on the management of important drug safety issues and to manage the dissemination of certain safety information through FDA's Web site to health care professionals and patients. Among other responsibilities described in more detail below, the Board and its staff:

- Identify, track, and oversee the management of important drug safety issues
 - Adjudicate organizational disputes concerning the management of drug safety issues
 - Establish policies regarding management of drug safety issues in CDER
 - Select drugs to be placed on Drug Watch and update their status (including deciding to remove drugs from Drug Watch) as appropriate
 - Oversee the development of patient and professional information sheets in CDER
 - Track important emerging safety issues and ensure that they are resolved in a timely manner
 - Ensure that CDER decisions about a drug's safety benefit from the input and perspective of experts within and outside FDA who have not been directly involved in the ongoing premarket evaluation or postmarket surveillance activities with respect to that drug
-

DEFINITIONS

- **Important Drug Safety Issue:** A drug safety issue that has the potential to significantly alter the benefit/risk analysis for the drug or significantly affect physicians' decisions to prescribe the drug

to certain patients. Examples of important drug safety issues include identification of serious side effects after approval or from a new use, and new studies identifying different effects in a subpopulation of patients.

- **Drug Watch:** Information on the Web about drugs that FDA is actively evaluating to determine the meaning and potential consequences of early safety signals.
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REFERENCES

- Guidance for industry *FDA's "Drug Watch" for Emerging Drug Safety Information*
 - CDER MAPP 4151.2 *Documenting Differing Professional Opinions and Dispute Resolution – Pilot Program*
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ORGANIZATION

- **Membership**

The Center Director requests nominations for members (and one alternate for each member) from the directors of each organization represented on the DSB and recommends members to the FDA Commissioner. The Commissioner appoints members to the Board from those recommended by the Center Director. The Office of Special Health Issues (OSHI) in the Office of the Commissioner manages the process for engaging consumer/patient consultants.

Members are initially appointed to serve 18, 24, 30, or 36 month terms with subsequent terms set at 2 years. Appointments are scheduled so that no more than 1/3 of the Board membership will change at a time.

The CDER DSB includes representatives from various Center organizations, as follows:

- **Chair** – The Deputy Director, CDER, is the non-voting chair of the DSB
- **Voting Members**
 1. Three individuals and two alternates from each of the following Center organizations:
 - Office of Drug Safety (ODS)
 - Office of New Drugs (OND)
 2. One individual and one alternate from each of the following Center organizations:
 - Office of Counter Terrorism and Pediatric Drug Development (OCTAP)
 - Office of Compliance (OC)
 - Office of Pharmaceutical Science (OPS)
 - Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
 - Office of Biostatistics (OB)

3. One individual and one alternate from each of the following non-CDER organizations:

- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Non-FDA DHHS Agency (e.g., NIH)
- Non-DHHS health care providing Agency (e.g., VA, DoD)

- **Non-Voting Member**

The Director, Office of Medical Policy (OMP), in CDER serves as a nonvoting member because of current collateral duties within OND.

- **Consultants**

The DSB can engage consumer and patient representatives as consultants to present views regarding emerging drug safety issues.

- **Executive Director and Staff**

A small staff carries out all operational, administrative, and other functions of the DSB. The staff works with the appropriate program offices to frame and develop issues to be taken before the DSB. The staff is responsible for developing templates for presenting issues to the DSB. (Presentations should include clear position statements and options to be considered.) The staff is also responsible for developing patient and professional safety information.

The staff operates under the supervision and oversight of an Executive Director, who is appointed by the Director, CDER. The Executive Director serves as the non-voting Executive Secretary to the DSB and is responsible for all staff activities.

- **Subcommittees and Working Groups**

1. The DSB may form subcommittees or working groups to review scientific issues, make recommendations, or implement activities related to the function of the DSB. Chairs, co-chairs, and members of subcommittees and working groups need not be members of the DSB, but will be selected by the DSB.
2. A Drug Watch Subcommittee, consisting of the DSB Chair and no more than five additional members, enables timely decision-making on placement of drugs on Drug Watch and addition or deletion of information (including removal of a drug from the Watch) based on predetermined criteria. Decisions of the Drug Watch Subcommittee are reviewed monthly by the full DSB.
3. When possible, the DSB will draw upon existing CDER/FDA working groups and committees and coordinate with ongoing activities.

RESPONSIBILITIES

- **The DSB and its staff will:**

1. Oversee the management of important drug safety issues, including:
 - Identification of emerging and ongoing important drug safety issues
 - Tracking the management of these issues with regular Board updates
 - Oversight of management approaches to important drug safety issues. If the Board does not concur with a management approach being taken, it may vote to recommend a different course of action.
 - Convening meetings to obtain information about the issues and developing advice for the Center Director on how to resolve the issues
 - Resolving disputes between organizations over approaches to drug safety (as opposed to individual differences of professional opinion (DPO) which are resolved through the process described in MAPP 4151.2)
 - Evaluating program recommendations for MedGuides to determine the need for specific MedGuides
2. Develop and document Center-wide drug safety policies (e.g., consistent standards for safety-related labeling decisions, consistent standards for requiring MedGuides or physician prescribing information (PPIs)). As part of its ongoing activities, the Board will develop and maintain a list of policies and procedures related to drug safety that need to be developed or updated. The Board will prioritize these and, with the assistance of the staff, will oversee the development of policies through the usual policy development process to include the concurrence of the Center Director. The DSB will also oversee implementation when policies are adopted.
3. Select drugs and related information to be placed on the Drug Watch and update the Drug Watch (see guidance for industry *FDA's "Drug Watch" for Emerging Safety Information*), including determining when a drug should be removed from the Drug Watch
4. Develop patient and professional information sheets
5. Track important emerging safety issues and ensure that they are resolved in a timely manner
6. Ensure that CDER decisions about drug safety benefit from the input of experts from within and outside of FDA who have not been involved in the ongoing premarket evaluation or postmarket surveillance activities. In part, the membership of the DSB ensures such input. Furthermore, the Board has the authority to consult outside experts as it deems appropriate on specific matters.

- **The DSB Chair will:**

1. Ensure that DSB meetings are held, as appropriate
2. Formulate the agenda for each meeting
3. Chair meetings of the DSB
4. Ensure that decisions made by the Board are communicated to the Center Director and other relevant Center managers

5. Choose members of DSB subcommittees and working groups
 - **The Executive Director will:**
 1. Arrange and organize meetings. Issues to be brought before the DSB should be directed to the attention of the Executive Director (directly or through the DSB staff), who will schedule them in consultation with the Chair of the DSB.
 2. Supervise the DSB staff
 3. Serve as the primary point of contact for coordinating and responding to inquiries related to the activities of the Board
 4. Maintain files of DSB activities
-

PROCEDURES

- **Referrals to the DSB**
 - Any organizational unit in CDER may refer a drug safety issue to the DSB for assessment by submitting a request to the Executive Director (directly or through the DSB staff), who, in consultation with the Chair, prioritizes and organizes topics for the meeting agenda.
 - On a monthly basis, OND and ODS can nominate safety items to the Executive Director for DSB evaluation on the regular agenda.
 - OND and ODS will maintain lists of any ongoing (i.e., unresolved) “important drug safety issues,” to include a description of each issue’s current management approach, using a defined template. Updated lists will be submitted to the Executive Director of the DSB on a monthly basis. The Board will review these issues on an ongoing basis and may request presentation of an issue for evaluation.
 - OND and ODS will refer emerging important drug issues in a timely manner to the Executive Director for consideration for placement on the Drug Watch.
 - The Therapeutic Inequivalence Action Coordinating Committee (TIACC) will refer unresolved therapeutic inequivalence issues to the Executive Director to evaluate for discussion by the DSB.
 - Recommendations and questions about requiring MedGuides will be referred to the Executive Director for discussion by the DSB. Usually, OND will be the referring office; however, any CDER office may make such a referral.
 - The DSB will develop and maintain templates for presentation of the data and for evaluation of recommendations.
- **Decision Making**

- Decisions made by the DSB will serve as recommendations to the Center Director.
 - Most recommendations are expected to be reached through consensus. When consensus cannot be reached, a vote will be taken.
 - Eleven members, with at least two members each from ODS and OND, constitute a quorum.
 - Recommendations will be made by a 2/3 majority of a quorum.
 - If a vote is closer than a 2/3 majority, no recommendation will be forwarded, but the Center Director will take the points of discussion into account in any decision to be made.
 - Decisions made by the Center Director, based on recommendations made by the DSB, will be implemented through the appropriate program office. For example, if the Center Director decides, on the basis of a DSB recommendation, that an Advisory Committee meeting should be held, the organization that would ordinarily be responsible will carry out the activity.
 - The Center Director retains final authority for Center decisions. All recommendations of the DSB may be appealed to the Center Director by the dissenting Office Director before the Center Director makes a final decision.
- **Conflict of Interest**
 - All non-FDA members will be screened for conflicts of interest related to the matters before the DSB.
-

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Guidance

FDA's "Drug Watch" for Emerging Drug Safety Information

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Deborah Henderson, (301) 594-5400.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**May 2005
Drug Safety**

Guidance

FDA's "Drug Watch" for Emerging Drug Safety Information

Additional copies are available from:

*Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210*

*5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573*

(Internet) <http://www.fda.gov/cder/guidance/index.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**May 2005
Drug Safety**

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Guidance¹

FDA's "Drug Watch" For Emerging Safety Information

This guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance on how FDA intends to develop and disseminate important emerging drug safety information concerning marketed drug products² to healthcare professionals and patients. This information will appear on an FDA Web page to be called the "Drug Watch."³

The Drug Watch is intended to identify drugs for which FDA is actively evaluating early safety signals. The Drug Watch is not intended to be a list of drugs that are particularly risky or dangerous for use; listing of a drug on the Drug Watch should not be construed as a statement by FDA that the drug is dangerous or that it is inappropriate for use. Rather, inclusion on the Drug Watch signifies that FDA is attempting to assess the meaning and potential consequences of emerging safety information.

All drugs have risks, and prescribers must balance the risks and benefits of a drug when making judgments about an individual patient's therapy. Sometimes after a drug is approved, rare but serious side effects emerge as the drug is more widely used or is prescribed for off-label uses. Sometimes emerging risks appear to be life-threatening, while in other cases they may appear to be less serious. In most instances, however, there is a period of uncertainty while FDA and the drug's sponsor evaluate new, emerging safety information to determine whether there is a real safety concern related to the drug and whether regulatory or other action is appropriate. The purpose of the Drug Watch Web page is to provide a forum in which we can communicate emerging safety information to the public while we continue to evaluate that information. We intend to work as quickly as possible to assess and address the potential safety issues identified on the Drug Watch.

¹ This guidance has been prepared by the Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

² The phrase *drug products* as used in this guidance includes all drug and biological products regulated by CDER. Marketed drugs included on the Drug Watch may be approved or unapproved drugs, used for approved or unapproved uses.

³ The Drug Watch page will be available at FDA's WEB site, www.fda.gov.

39 Moreover, we will continue to communicate important information about drug risks that are
40 known with greater certainty using traditional means, such as public health advisories.

41
42 FDA's guidance documents, including this guidance, do not establish legally enforceable
43 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
44 be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

45
46

47 **II. BACKGROUND**

48

49 FDA has long provided information on drug risks and benefits to healthcare professionals and
50 patients when that information has generated a specific concern or prompted a regulatory action,
51 such as a labeling change. Because of recent questions related to drug safety, however, FDA is
52 reexamining its risk communication program, including how and when we communicate emerging
53 risk information to healthcare professionals and patients.

54

55 Increasingly, patients are taking a more active role in their healthcare. Patients want information
56 about the products they are taking, and patients actively seek the information they want from
57 different sources, including, for example, the Internet. Patients and their healthcare providers rely
58 on the information from these sources to make important prescribing and treatment decisions.
59 FDA has concluded it should do more to make drug risk information available as it emerges while
60 the Agency is evaluating its significance. We want to make sure that patients and their healthcare
61 providers have quick access to the most up-to-date and emerging product information available in
62 an easily accessible form. As a result, we are taking steps, described below, to make important
63 emerging drug safety information available to healthcare professionals and patients in a new
64 format and earlier than we have in the past. Our goal with the Drug Watch is to share emerging
65 safety information before we have fully determined its significance or taken final regulatory action
66 so that patients and healthcare professionals will have the most current information concerning the
67 potential risks and benefits of a marketed drug product upon which to make individual treatment
68 choices.

69

70

71 **III. DISCUSSION**

72

73 **A. What information will be posted?**

74

75 We have decided to develop a page on our Web site, known as the "Drug Watch," that will provide
76 information about drugs with significant emerging safety issues that FDA is evaluating. The
77 factors FDA intends to consider in determining whether to post such information about a drug on
78 the Drug Watch are described in section III.B., below.

79

80 For some drugs, the Web page will contain factual information about newly observed, serious
81 adverse events associated with the use of a drug that have been reported to FDA.

82

83 For example FDA might post the following for Drug A:

84

Draft — Not for Implementation
Contains Non-binding Recommendations

85 FDA is investigating postmarketing reports of renal failure in elderly patients treated
86 with Drug A, but a causal relationship has not been established. We are continuing to
87 analyze these reports to determine whether the occurrence of these adverse events
88 affects the risk/benefit assessment of Drug A therapy.
89

90 Although sponsors are likely to be aware of these emerging potential safety issues, often patients
91 and healthcare professionals do not become aware of the emerging information until we or the
92 sponsors take some action.⁴ Posting this information on the Web site will alert patients and
93 healthcare professionals to potential safety risks while FDA is still evaluating the strength of the
94 relationship between the drug and the adverse event.
95

96 For other drugs, the Web page may contain information about significant emerging risks that FDA
97 believes may be associated with a drug, but that might be avoided by appropriate patient selection,
98 monitoring, or use of concomitant therapy. This type of information is illustrated by the following:
99

100 Drug B has been associated with serious skin reactions in patients allergic to eggs.
101 Prescribers should consider this information when treating patients with these allergies.
102

103 A third category of information might be posted on the Drug Watch when an important risk
104 minimization procedure is put into place by a sponsor in response to emerging information.
105 Announcing the new procedure on the Drug Watch will alert patients and healthcare professionals
106 to important changes in how a drug should be prescribed, dispensed, or used. For example:
107

108 The sponsor for Drug C has determined that Drug C can cause liver damage in patients
109 with impaired liver function. The sponsor has advised prescribers to check a patient's
110 liver enzymes before the drug is prescribed and at regular intervals thereafter.
111

112 Most of the information that will be posted on our Web site is information that is now made
113 available to the public (after proper redaction of confidential commercial and personal privacy
114 information) in response to Freedom of Information Act (FOIA) requests. Because of the
115 importance of this information to healthcare professionals and patients, we have decided to take
116 steps to make such emerging information available without waiting for a FOIA request, even
117 before we have reached conclusions about that information that might prompt a regulatory action
118 (such as relabeling the drug).
119

120 For emerging safety information that we are still evaluating, we will accompany the information
121 with a disclaimer such as the following: "This information reflects FDA's preliminary analysis
122 of data concerning this drug. FDA is considering, but has not reached a final conclusion about,
123 this information. FDA intends to update this web page when additional information or analyses
124 become available."
125

⁴ Sponsors are the most frequent source of reported information about serious side effects, and FDA regularly discusses emerging risk information with sponsors to further its evaluation of the information and determine an appropriate course of action. The purpose of the Drug Watch is to disseminate this information to the public while FDA evaluates it so that patients and practitioners may consider the information as well.

126 As part of implementing the Drug Watch, we also intend to provide information about the status of
127 our analysis of an emerging safety issue. We might say, for example, that we have not yet
128 determined whether the reported side effects have been caused by the drug, but we are continuing
129 to analyze the data. In other instances, we might say that we have concerns and intend to take the
130 issue to a public advisory committee. We intend to update the information on the Drug Watch
131 frequently as new information becomes available or specific issues are resolved.⁵
132

133 As noted, the purpose of the Drug Watch Web page is to communicate significant emerging safety
134 information about specific drug products or classes of drug products. This emerging safety
135 information may relate to new risks, new information on known risks, or risks associated with off-
136 label uses. By definition, however, the information posted on the Drug Watch is information about
137 which FDA has made no final regulatory judgment. Posting information on the Drug Watch Web
138 page does not mean that FDA has concluded there is a causal relationship between the drug
139 product and the risks or adverse events described. Such posting also does not mean FDA is
140 advising practitioners to discontinue prescribing the products that appear on the Drug Watch.
141 Instead, our goal is to make emerging safety information available to the public so that healthcare
142 professionals and patients can consider the information when making decisions about a patient's
143 medical treatment.
144

145 Information will be posted with or without redactions in accordance with applicable disclosure
146 laws and FDA regulations.
147

B. How will FDA decide which drugs will be included on the Drug Watch?

148
149
150 FDA has identified several factors that it plans to consider when deciding which drug products
151 and information to include on the Drug Watch:
152

⁵ We also have decided to intensify our current program to provide the public with the most important information for the safe and effective use of drugs in patient friendly language. As part of this continuing effort, we are developing *Patient Information Sheets* intended to convey critical facets of a product's approved labeling in lay terms. These sheets will include a section for "emerging safety information" in those instances when we determine that there is information on the Drug Watch that a patient should consider. This "emerging safety information" will match the information on the Drug Watch. Information from the Drug Watch that is not in the final labeling of the product will be clearly delineated and segregated along with 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 sheet when additional information or analyses become available." Our ultimate objective is to develop Patient Information Sheets for all approved drugs, most of which will not have an emerging safety section.

We are also continuing to develop *Healthcare Professional Information Sheets*, which we ultimately intend to develop for all new molecular entities as well as some other drugs. These sheets are intended to highlight the most up-to-date information healthcare professionals may want to consider when prescribing drugs for their patients. This is not a new approach. When available, the highlights section of a product's approved labeling will be used to develop the Healthcare Professional Information sheets. We have already posted some patient and healthcare professional information sheets on our Web site for drugs with recent emerging safety issues. See for example, Celebrex patient and professional sheets, <http://www.fda.gov/cder/drug/infopage/celebrex/Celebrex-ptsk.pdf> and <http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf>. We intend to link the information that is on Drug Watch to patient and healthcare professional information sheets when they are available.

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153 • Whether new and emerging safety information could significantly affect prescribing
154 decisions or how patients should be monitored (e.g., a drug that has been identified with a
155 possible association with renal failure should not be prescribed to patients with renal
156 disease; a new possible drug-drug interaction has been identified and needs to be
157 considered in prescribing)

158 • Whether measures can be taken as a result of providing information that could help to
159 prevent or mitigate harm (e.g., limit prescribing to patients most likely to benefit from the
160 drug, conduct special monitoring of patients on the drug, be alert for signs of serious
161 adverse reactions)

162 • Whether an unapproved (off-label) use of the drug appears to pose a significant risk to
163 patients

164
165 We may also consider other factors as appropriate.

166
167 Before posting information on the Drug Watch, we plan to conduct at least a preliminary analysis
168 to determine that the new safety information is sufficiently credible to warrant public
169 dissemination. We intend to post emerging information about a drug on the Drug Watch only
170 when we believe that the data are significant enough to warrant further consideration to determine
171 whether an actual safety problem exists.

172
173 We have established a Drug Safety Oversight Board that will be responsible for managing
174 important emerging drug safety issues in the CDER and the Drug Watch program. This Board will
175 decide which products (or classes of products) to include on the Drug Watch using the preceding
176 factors, and, using the factors described below, will determine when drugs are removed from the
177 Drug Watch. The Board will also manage the process for determining what information will
178 appear on the site with regard to particular drugs.

179
180 The Board will include representation from the following CDER Offices:

- 181
- 182 • Office of Drug Safety
 - 183 • Office of New Drugs
 - 184 • Office of Counter Terrorism and Pediatric Drug Development
 - 185 • Office of Medical Policy
 - 186 • Office of Compliance
 - 187 • Office of Pharmaceutical Sciences
 - 188 • Office of Clinical Pharmacology and Biopharmaceutics
 - 189 • Office of Biostatistics
- 190

191 In addition, the Board will have a permanent member from outside of CDER from each of the
192 following:

- 193
- 194 • FDA's Center for Biologics Evaluation and Research
 - 195 • FDA's Center for Devices and Radiological Health,

- 196 • A non-FDA Department of Health and Human Services (DHHS) agency (e.g., the National
197 Institutes of Health)
198 • A non-DHHS healthcare providing agency (e.g., the Veterans Administration or the
199 Department of Defense).
200

201 The Board also may engage as consultants the Chairs of FDA Advisory Committees and other
202 external scientific experts, as well as consumer and patient representatives to present their views
203 regarding emerging drug safety issues.
204

205 **C. How will drugs be removed from the Drug Watch?**
206

207 FDA plans to regularly update the information on the Drug Watch Web page as new information
208 becomes available. As safety issues are resolved, FDA intends to promptly remove drugs from the
209 Drug Watch. For example, a drug may be removed from the Drug Watch when its labeling has
210 been revised to address the safety concerns, when FDA has taken other steps to adequately
211 communicate information to healthcare professionals and patients, or when FDA has determined
212 that, despite the initial signals, there is no new safety concern.
213

214 **D. Will sponsors be notified that a drug will be placed on the Drug Watch?**
215

216 FDA intends to notify the relevant sponsor that information about its drug will be placed on the
217 Drug Watch shortly before the first instance in which information about that drug is posted on the
218 web site.
219

220 **E. How will the Drug Watch affect the promotion of prescription drugs?**
221

222 FDA recognizes that some sponsors may consider drawing promotional comparisons between their
223 products and products that appear on the Drug Watch (e.g., by suggesting that the appearance of a
224 drug on the Drug Watch necessarily signals a serious problem and/or by using the information
225 posted on the Drug Watch as the basis for a comparative claim). In turn, some sponsors whose
226 products appear on the Drug Watch may want to minimize the effects of the information that FDA
227 has made public.
228

229 We remind sponsors that all safety and effectiveness claims made in prescription drug promotion,
230 including claims based on government materials such as the Drug Watch, must be supported by
231 substantial evidence or substantial clinical experience, and must not be otherwise false or
232 misleading (21 U.S.C. 355 and 352; 21 CFR 202.1(e)).
233

234 Neither the fact that a drug appears on the Drug Watch nor the specific information posted about
235 that drug will generally constitute (either separately or collectively) substantial evidence or
236 substantial clinical experience to support a comparative safety or effectiveness claim. Therefore,
237 comparative claims made in prescription drug promotion based on information on the Drug Watch
238 (e.g., "Our drug is safer because of the adverse event information posted on the Drug Watch about
239 a competitor's drug"; or, "Our drug is safer because it is not on the Drug Watch") may be
240 considered false or misleading.
241

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242 Representations made to minimize the effect of emerging risk information on the site may also be
243 considered false or misleading. For those seeking to explain to healthcare professionals what, if
244 anything, it means to appear on the Drug Watch, we refer you to the sections of this guidance that
245 discuss the purpose of the Drug Watch Web page and the nature of the information to be posted on
246 the site.