

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2009-N-0138]

Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committees: Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee.

General Function of the Committees: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on June 29 and 30, 2009, from 8 a.m. to 5 p.m.

Addresses: Electronic comments should be submitted to <http://www.regulations.gov>. Enter "FDA-2009-N-0138 Liver Injury Related to the Use of Acetaminophen" and follow the prompts to submit your statement. Written comments should be submitted to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments received will be posted without change, including any personal information provided. Comments received on or before June 8, 2009, will be provided to the committee before the meeting.

Location: Marriott Conference Centers, University of Maryland, University College Inn and Conference Center, 3501 University Blvd. East, Adelphi, MD. The Conference Center telephone number is 301-985-7300.

Contact Person: Elaine Ferguson, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301-827-7001, FAX: 301-827-6776, e-mail: elaine.ferguson@fda.hhs.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), codes 3014512535, 3014512541, and

3014512529. Please call the Information Line for up-to-date information on this meeting. A notice in the **Federal Register** about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the agency's Web site and call the appropriate advisory committee hot line/phone line to learn about possible modifications before coming to the meeting.

Agenda: The primary topic area for discussion is how to address the public health problem of liver injury related to the use of acetaminophen in both over-the-counter (OTC) and prescription (Rx) products. FDA recognizes that acetaminophen is an important drug used to treat pain and fever in both settings and is not seeking to remove it from the market. The risk of developing liver injury to the individual patient who uses the drug according to directions is very low. However, acetaminophen containing products are used extensively making the absolute number of liver injury cases a public health concern.

More complete information about the topics on which FDA will seek public input will be available by or around May 22, 2009, at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>, click on the year 2009 and scroll down to the appropriate advisory committee link.

FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting. Background material is available at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>, click on the year 2009 and scroll down to the appropriate advisory committee link.

Background: Acetaminophen is one of the most commonly used drugs in the United States,¹ yet it is also an important cause of serious liver injury. Acetaminophen is the generic name of a drug found in many common brand name over-the-counter (OTC) products, such as Tylenol, and Prescription (Rx) products, such as Vicodin and Percocet. Acetaminophen is an important drug, and its effectiveness in relieving pain and fever is widely known. Unlike other

commonly used drugs to reduce pain and fever (e.g., nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin, ibuprofen, and naproxen), at recommended doses acetaminophen does not cause adverse effects, such as stomach discomfort and bleeding, and acetaminophen is considered safe when used according to the directions on its OTC or Rx labeling. However, taking more than the recommended amount can cause liver damage, ranging from abnormalities in liver function blood tests, to acute liver failure, and even death. Many cases of overdose are caused by patients inadvertently taking more than the recommended dose (i.e., 4 grams a day) of a particular product, or by taking more than one product containing acetaminophen (e.g., an OTC product and an Rx drug containing acetaminophen).

The mechanism of liver injury is not related to acetaminophen itself, but to the production of a toxic metabolite. The toxic metabolite binds with liver proteins, which cause cellular injury. The ability of the liver to remove this metabolite before it binds to liver protein influences the extent of liver injury. In a study that combined data from 22 specialty medical centers in the United States, acetaminophen-related liver injury was the leading cause of acute liver failure for the years 1998 through 2003.² Patients in this study were found to have taken too much acetaminophen from OTC, Rx products, or both. Almost half of these cases involved overdose in which the patient had not intended to take too much acetaminophen (unintentional overdoses), although many cases of liver injury with acetaminophen result from self-harm, i.e., intentional self-poisoning. The high percentage of cases of liver failure related to unintentional acetaminophen overdose was also observed in a study published in 2007.³ The extent of liver failure cases reported in the medical literature provides an important signal of concern. However, the types of databases available to identify cases make it difficult to determine the full extent of the problem or whether interventions have been successful.

² Larson, A.M., J. Polson, R.J. Fontana, et al., Acute Liver Failure Study Group (ALFSG), "Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study," *Hepatology* 2005, Dec;42(6):1364-72.

³ Bower, W.A., M. Johns, H.S. Margolis, et al., "Population-Based Surveillance for Acute Liver Failure," *The American Journal of Gastroenterology* 2007;102:2459-63.

¹ Kaufman, D.W., J.P. Kelly, L. Rosenberg, et al., "Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States: The Slone Survey," *The Journal of the American Medical Association* 2002, Jan 16;287(3) 337-44.

A. Why Acetaminophen Overdoses Occur

There are few data available describing consumer behavior with acetaminophen products or consumer understanding of acetaminophen toxicity. However, based on the prevalence of liver injury, it appears that there are distinct factors associated with acetaminophen and acetaminophen products that contribute to this public health problem. These factors are listed below.

- Taking just a small amount of acetaminophen over the recommended total daily dose (4 grams per day) may lead to liver injury.⁴

Currently recommended doses and tablet strengths of acetaminophen leave little room for error and the onset of liver injury can be hard to recognize. There is scientific agreement that taking a large amount of acetaminophen over a short period of time causes liver injury, but there is limited agreement as to the specific threshold dose for toxicity. In addition, the onset of symptoms associated with acetaminophen liver injury can take several days, even in severe cases. The symptoms of liver injury may not be readily identified by an individual because they may be non-specific and mimic flu symptoms. The antidote for acetaminophen poisoning, N-acetylcysteine, is less effective when liver injury has progressed too far.

- Some individuals may be especially sensitive to liver injury from acetaminophen. The maximum safe dose may not be the same for all persons. Individuals with increased sensitivity may experience toxic effects at lower acetaminophen doses.

Available information suggests that some individuals, such as those who use alcohol or have liver disease, may have a greater sensitivity to the effects of the toxic metabolite because they produce more or are unable to clear it from the body as easily. More research is needed to understand whether ethnicity, genetics, nutrition, or other factors might have a role in making some individuals more sensitive.

- There is a wide array of OTC and Rx acetaminophen products used in a range of doses for various indications. For some people, it may be difficult to identify the appropriate product to use. Acetaminophen is in many widely used OTC single ingredient products, such as those to treat headaches, and multiple ingredient (combination) products, such

as those to treat symptoms of the common cold, like aches and fever.

Acetaminophen is also a component of a number of Rx drug products in combination with narcotic pain medicines. So, consumers may reasonably attempt to treat different conditions or symptoms with multiple choices among products containing acetaminophen, but may not realize that acetaminophen is an ingredient common to each.

- It can be difficult to identify acetaminophen as an ingredient. Rx products that contain acetaminophen (usually with codeine or oxycodone) are often labeled as containing "APAP" on pharmacy dispensed containers.⁵ Without clear labeling, patients may take more than one product containing acetaminophen (e.g., a Rx product and an OTC product) without realizing it, and in some cases take a harmful overdose.

- Multiple products exist for children containing different strengths. Liquid acetaminophen formulations intended for use in infants are typically more concentrated (i.e., stronger) to enable proper dosing using less liquid. However, failure to distinguish between the two strengths of liquid can result in an accidental overdose where the parent gives a higher dose of the concentrated drops to a younger child.

- The association between acetaminophen and liver injury is not common knowledge.⁶ Consumers are not sufficiently aware that acetaminophen can cause serious liver injury, and their perceptions may be influenced by the marketing of the products. Finding ways to educate consumers about the risk of liver injury from acetaminophen has been difficult. Current labeling on OTC products may be overlooked, as can the patient information provided with dispensed prescriptions. Programs to educate the public about safe use of acetaminophen have been small and encountered a number of obstacles. Advertisements of OTC drugs often emphasize the effectiveness of products, but are not subject to the same requirements to offset such messages by providing warning information as prescription products. Also, acetaminophen is available in retail outlets in large quantities (e.g., 500 tablets per bottle) which may contribute to the perception

that the ingredient is unlikely to be harmful.

B. FDA's Previous Actions

In the late 1990s, research began to show that acetaminophen was a major cause of acute liver failure in the United States, with up to half of the cases due to accidental overdose. Responding to these concerns, FDA took a number of steps to reduce the incidence of liver injury related to acetaminophen.

In 1998, FDA finalized a regulation that required all OTC acetaminophen products to include an alcohol warning in labeling. The warning stated: Acetaminophen. "Alcohol Warning" [heading in boldface type]: "If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage."

In 2002, FDA convened an Advisory Committee meeting to discuss unintentional liver toxicity related to the use of OTC acetaminophen.⁷ The Advisory Committee recommended a specific liver toxicity warning and distinctive labeling on OTC packages so that products containing acetaminophen could be more easily identified. FDA and manufacturers were also advised to educate consumers and health professionals about the risk of liver injury from acetaminophen.

In early 2004, FDA launched a public education campaign to help consumers use acetaminophen more safely. By most standards, the campaign would be considered small, due to budgetary constraints. It was also limited by reluctance on the part of some commercial outlets to provide a venue for FDA's message about acetaminophen toxicity as the product was sold or promoted in those outlets. Nonetheless, FDA has continued to expand efforts to improve public education about acetaminophen overdosing and liver injury and has recently updated the acetaminophen information on FDA's Web site.

In 2004, FDA sent letters to every state board of pharmacy asking them to consider requiring labeling on the immediate container of Rx products containing acetaminophen that: (1) uses the term acetaminophen, not APAP, (2) instructs patients to avoid concurrent use of other acetaminophen containing drugs, (3) instructs patients not to exceed the maximum daily recommended acetaminophen dose, and (4) instructs patients to avoid drinking

⁴Data from both FDA's Adverse Event Reporting System (AERS) and the ALFSG show that the median daily dose of acetaminophen related to liver injury was 5 to 7.5 grams/day, very near the current maximum daily dose of 4 grams/day.

⁵"APAP" is an acronym based on the chemical name of acetaminophen, N-acetyl-para-aminophenol.

⁶Stumpf J.L., A.J. Skyles, C. Alaniz, et al., "Knowledge of Appropriate Acetaminophen Doses and Potential Toxicities in an Adult Clinic Population," *Journal of the American Pharmacists Association* (2003), 2007 Jan-Feb; 47(1): 35-41.

⁷See <http://www.fda.gov/OHRMS/DOCKETS/98fr/082002c.htm>.

alcohol during prescription use.⁸ FDA was informed by the National Association of Boards of Pharmacy that, as of February 2008, no states had implemented regulations related to the request.

In December 2006, FDA issued proposed regulations for OTC labeling for acetaminophen containing products to require inclusion of new safety information and that the container and outer carton identify acetaminophen when it is an ingredient.⁹ The final version of the regulation is currently under review.

In 2007, the Director of FDA's Center for Drug Evaluation and Research (CDER) convened a multidisciplinary working group in CDER to continue to evaluate the issues associated with acetaminophen-related liver injury and consider additional steps FDA could take to decrease the number of cases of acetaminophen-related liver injury. The working group considered detailed reviews of the issues from the Office of Nonprescription Products, the Office of Surveillance and Epidemiology and the Division of Anesthesia and Analgesic and Rheumatology Drug Products as part of its deliberations. The working group considered the full range of options proposed and made recommendations to the Center Director regarding which should be considered for implementation. Given the complex nature of the underlying problem of acetaminophen liver toxicity, the Center Director and the Working Group agreed that the options should be presented for public discussion prior to taking further action. The report of the Working Group will be available by or around May 22, 2009, at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>, click on the year 2009 and scroll down to the appropriate advisory committee link.

Procedure: Interested persons and Sponsors (representatives from industry) may present data, information, or views, orally or in writing, on issues pending before the committee.

All electronic and written submissions submitted to the Docket (see above section: *Addresses*) on or

⁸ Letter from Steven Galson to State Boards of Pharmacy, *Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-Related Gastrointestinal and Renal Toxicity* (January 22, 2004), available on FDA's Web site at <http://www.fda.gov/cder/drug/analgesics/letter.htm>.

⁹ Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the Counter Human Use: Proposed Amendment of the Tentative Final Monograph: Required Warnings and Other Labeling, 71 FR 77314-52 (December 26, 2006) (Docket No. 1977N-0094L) (amending 21 CFR 201.66, 201.322, 201.325, 343.50).

before June 8, 2009, will be provided to the committees.

Oral presentations from the public (excluding Sponsors) will be scheduled between approximately 1 p.m. to 2 p.m. on both days. Persons desiring to make formal oral presentations during this time should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before June 1, 2009. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak at the open public hearing session by June 3, 2009.

FDA will work with sponsors of acetaminophen products who wish to make presentations to ensure that adequate time, separate from the 1 p.m. to 2 p.m. time slots for the general Open Public Hearing, is provided. Sponsors interested in making formal presentations to the committees should notify the contact person on or before June 1, 2009. Sponsors with common interest are urged to coordinate their oral presentations.

Persons attending FDA's advisory committee meetings are advised that the agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact Elaine Ferguson at least 7 days in advance of the meeting.

FDA is committed to the orderly conduct of its advisory committee meetings. Please visit our Web site at <http://www.fda.gov/oc/advisory/default.htm> for procedures on public conduct during advisory committee meetings.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app.).

Dated: April 16, 2009.

Randall W. Lutter,
Deputy Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

National Center for Injury Prevention and Control, Initial Review Group, (NCIPC, IRG)

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92-463), CDC announces the following meeting of the aforementioned review group:

Times and Dates:

10 a.m.–10:10 a.m., May 18, 2009 (Open).

10:10 a.m.–4 p.m., May 18, 2009 (Closed).

Place: Teleconference, Toll Free: (877) 468-4185, Participant Passcode: 4475689.

Status: Portions of the meetings will be closed to the public in accordance with provisions set forth in Section 552b(c)(4) and (6), Title 5, U.S.C., and the Determination of the Director, Management Analysis and Services Office, CDC, pursuant to Section 10(d) of Public Law 92-463.

Purpose: This group is charged with providing advice and guidance to the Secretary, Department of Health and Human Services, and the Director, CDC, concerning the scientific and technical merit of grant and cooperative agreement applications received from academic institutions and other public and private profit and nonprofit organizations, including State and local government agencies, to conduct specific research that focuses on prevention and control.

Matters To Be Discussed: The meeting will include the review, discussion, and evaluation of applications submitted in response to Fiscal Year 2009 Requests for Applications related to the following individual research announcement: TS09001, Libbey Montana Amphibole Epidemiology Research Program (R01) and TS09002, Disease Progression in persons Exposed to Asbestos Contaminated Vermiculite Ore in Marysville, Ohio (R01).

Agenda items are subject to change as priorities dictate.

Contact Person for More Information: Lisa T. Garbarino, B.S., NCIPC, Division of Injury Response, CDC, 4770 Buford Highway, NE., M/S F62, Atlanta, Georgia 30341, Telephone (440) 723-1527. The Director, Management Analysis and Services Office has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities for both CDC and the Agency for Toxic Substances and Disease Registry.

Dated: April 16, 2009.

Elaine L. Baker,
Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.

[FR Doc. E9-9470 Filed 4-23-09; 8:45 am]

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