DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 343

[Docket No. 1977N–0094L]

RIN 0910–AF36

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its over-the-counter (OTC) labeling regulations and the tentative final monograph (TFM) for OTC internal analgesic, antipyretic, and antirheumatic (IAAA) drug products to include new warnings and other labeling requirements advising consumers about potential risks and when to consult a doctor. FDA is also proposing to remove the alcohol warning in its regulations and add new warnings and other labeling for all OTC IAAA drug products. The new labeling would be required for all OTC drug products containing an IAAA active ingredient whether marketed under an OTC drug monograph or an approved new drug application (NDA). FDA is issuing this proposal as part of its ongoing review of OTC drug products after considering the advice of its Nonprescription Drugs Advisory Committee (NDAC) and other available information. FDA is proposing these labeling changes because it has tentatively concluded they are necessary for these ingredients to be considered

generally recognized as safe and effective and not misbranded for OTC use. FDA will address information about the cardiovascular risks of nonsteroidal anti-inflammatory drugs (NSAIDs) that was discussed at a February 16–18, 2005, FDA advisory committee meeting, and the ''Allergy alert'' warning for NSAID products, in a future issue of the **Federal Register**.

DATES: Submit written or electronic comments, including comments on FDA's economic impact determination, by [*insert date 150 days after date of publication in the* **Federal Register**]. The specified comment period is longer than is normally provided for proposed rules. Because of the complexity of the proposed rule, FDA is providing an additional 60 days (beyond the normal comment period) for comments to be submitted and does not plan to extend the comment period beyond this date. Please see section XV of this document for the proposed effective and compliance dates of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 1977N–0094L and Regulatory Information Number (RIN) 0910–AF36 by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.

- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No. and RIN for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Marina Chang, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD, 20993–0002, 301–796–2090.

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I. Introduction

FDA is proposing to: (1) Amend the TFM for OTC IAAA drug products, (2) remove the alcohol warning, and (3) add new warnings and other labeling for all OTC IAAA drug products. The proposed warnings and other labeling requirements will advise consumers of potential risks and when to consult a doctor. More specifically, FDA is proposing the following changes to the labeling:

- Requiring a new liver warning for products that contain acetaminophen.

- Requiring a new stomach bleeding warning for products that contain an NSAID (e.g., aspirin or ibuprofen).

- Removing the alcohol warning currently required for all OTC IAAA drug products in § 201.322 (21 CFR 201.322) and incorporating an alcohol warning in the new liver warning for acetaminophen and the new stomach bleeding warning for NSAIDs.

- Requiring that the ingredient acetaminophen be prominently identified on the product's principal display panel (PDP) of the immediate container and the outer carton, if applicable.

- Requiring that the name of the NSAID ingredient followed by the term ''NSAID'' be prominently identified on the product's PDP of the immediate container and the outer carton, if applicable.

This new labeling would be required for all OTC drug products containing an IAAA active ingredient, whether marketed under an OTC drug monograph or an approved NDA. FDA bases this proposal on its reviews of the medical literature, data provided to FDA, and recommendations made by NDAC. FDA has tentatively concluded that new labeling for OTC IAAA drug products is necessary for the safe and effective use of these products by consumers.

II. Background

FDA believes that acetaminophen and NSAIDs, when labeled appropriately and used as directed, are safe and effective OTC drug products that benefit tens of millions of consumers every year. FDA believes that these products should continue to be accessible to consumers in the OTC setting.

- Internal analgesics have long been very effective OTC drug products for the intermittent treatment of minor aches and pains and fever.

- At their recommended OTC doses, these products are only rarely associated with serious adverse events relative to the number of consumers who use these products.

A. Development of OTC IAAA Drug Product Warnings

The development of a monograph for OTC IAAA drug products began in 1977 with publication of an expert panel report and continued in 1988 with publication of the TFM. The development of labeling for OTC IAAA drug products is recorded in the following documents.

1. Warnings for Aspirin and Acetaminophen

In the **Federal Register** of July 8, 1977 (42 FR 35346), FDA published the report of the Advisory Review Panel on OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products (the IAAA Panel) for OTC IAAA active ingredients: Acetaminophen, aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate. The recommendations included labeling and warnings for:

- *Aspirin*: ''Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician'' (42 FR 35346 at 35387), and
- *Acetaminophen*: ''Do not exceed recommended dosage because severe liver damage may occur'' (42 FR 35346 at 35415).

In the **Federal Register** of November 16, 1988 (53 FR 46204), FDA published a tentative monograph with the following warnings for:

- *Aspirin*: ''Do not take this product if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor'' (53 FR 46204 at 46256), and

- *Acetaminophen*: ''Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.'' This warning follows the general overdose warnings in 21 CFR 330.1(g) (53 FR 46204 at 46213).

2. Warnings in the Professional Labeling for Aspirin

In the **Federal Register** of October 23, 1998 (63 FR 56802), FDA published labeling for health professionals (not available in OTC drug product labeling) that provided for cardiovascular and rheumatologic indications. The labeling listed adverse reactions reported in the literature, e.g., hypotension (low blood pressure); tachycardia (rapid heart rate); dizziness; headache; dyspepsia (indigestion); bleeding, ulceration, and perforation of the gastrointestinal (GI) tract; nausea; and vomiting. FDA determined that consumers were not able to determine when they needed to take aspirin to prevent cardiovascular events, such as stroke, myocardial infarction (damage to the heart muscle), or other conditions. FDA did not consider it possible to provide adequate directions and warnings to enable the layperson to make a reasonable self-diagnosis of these cardiovascular and rheumatologic conditions.

3. Alcohol Warnings for Acetaminophen and NSAIDs

In the **Federal Register** of October 23, 1998 (63 FR 56789), FDA published a final regulation stating that any OTC drug product, labeled for adult use, containing acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate must bear an alcohol warning statement in its labeling. Section 201.322 requires the following statements:

- *For products containing acetaminophen*:

Alcohol Warning: 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.

- *For products containing aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate*:

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take (name of active ingredient) or other pain relievers/fever reducers. (Name of active ingredient) may cause stomach bleeding.

- *For products containing acetaminophen with other IAAA active ingredients*:

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take (insert acetaminophen and one other IAAA active ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate) or other pain relievers/fever reducers. Acetaminophen and (insert name of one other IAAA active ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate) may cause liver damage and stomach bleeding.

4. Proposed Amendment to Include Ibuprofen as a Generally Recognized Safe and Effective OTC IAAA Active Ingredient

In the **Federal Register** of August 21, 2002 (67 FR 54139), FDA proposed to include ibuprofen in the monograph for OTC IAAA drug products with additional warnings:

Ask a doctor before use if you have:

- Problems or serious side effects from taking pain relievers or fever reducers
- Stomach problems that last or come back, such as heartburn, upset stomach, or pain
- Ulcers
- Bleeding problems
- High blood pressure, heart or kidney disease, are taking a diuretic, or are over 65 years of age.

FDA received several comments (Refs. 1 and 2) about the proposed warning for kidney disease and reopened the administrative record on June 4, 2003 (68 FR 33429), to allow for additional public comment. FDA continues to propose a warning about kidney disease for ibuprofen and other NSAIDs in this document. In a future issue of the **Federal Register**, we will publish our final decision about this warning and the proposed inclusion of ibuprofen in the monograph.

B. Completion of the OTC IAAA Drug Products FM

In the process of completing the FM for OTC IAAA drug products, FDA reviewed a variety of data regarding the safety of acetaminophen, aspirin, and other NSAIDs. FDA continued to receive serious adverse event reports associated with the use of these products during this review. These serious adverse events included unintentional acetaminophen hepatotoxicity and NSAID-related GI bleeding and renal toxicity. Although the occurrence of these events is rare, relative to the extensive use of the products, as described in the text that follows, FDA believes that labeling changes are necessary for the safe and effective use of these products and to reduce the associated morbidity.

1. Unintentional Acetaminophen Hepatotoxicity

Acetaminophen is widely available in numerous single ingredient and combination OTC drug products, and in many prescription drug products, as a pain reliever and/or fever reducer. OTC acetaminophen drug products, as currently labeled and used, have been reported to be associated with unintentional overdose that may lead to serious hepatotoxicity (Ref. 3). The IAAA Panel discussed overdose-related hepatotoxicity (42 FR 35346 at 35413 to 35414), and FDA addressed it in the IAAA TFM (53 FR 46204 at 46213 to 46218). (See section II.A.1 of this document.)

2. Aspirin and Other NSAIDs—GI Bleeding and Renal Toxicity

Aspirin and other NSAIDs are available OTC for the treatment of minor aches and pain, for the treatment of headaches, and for fever reduction. Per aspirin's professional labeling (not part of the OTC drug product labeling), aspirin may be used to reduce the risk of serious cardiovascular events when taken on a daily basis under the direction of a physician. Aspirin is also effective in treating a variety of rheumatologic diseases under the direction of a physician. The professional labeling also includes information about the potential risk of GI bleeding and renal toxicity associated with aspirin.

OTC nonaspirin salicylates include the NSAIDs ibuprofen, naproxen sodium, and ketoprofen. The product labels for these products are not required to contain warnings about GI bleeding and renal toxicity. These ingredients are, however, also available by prescription at strengths higher than in OTC products and the prescription product labeling contains warnings about these risks.

III. NDAC Meeting

At a September 19 and 20, 2002, meeting, NDAC considered products currently marketed with OTC IAAA ingredients, including acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate. FDA expressed its belief that these products should remain available OTC given their overall effectiveness and safety, the benefit to consumers of having a pain reliever and fever reducer available OTC, and the use of these products by tens of millions of people weekly. FDA suggested that certain interventions could decrease the frequency and morbidity of these serious adverse events. NDAC members were asked to consider which additional interventions were necessary to reduce the occurrence of serious adverse events. The presentations made at the meeting, and NDAC's findings, are summarized in this document. More information about the September 2002 NDAC meeting is available on the Internet and in the Division of Dockets Management (see **ADDRESSES**).

A. Data and Information Reviewed

FDA provided NDAC with the following data and information (Ref. 3):

- Applicable sections of rulemakings for OTC IAAA active ingredients.
- Proposed and final rules for the alcohol warning for OTC IAAA drug products.
- Final rule for professional labeling of OTC drug products containing aspirin.
- Amendment to propose inclusion of ibuprofen in the monograph for OTC IAAA drug products.
- For acetaminophen, FDA reviews of data, poisoning data in Toxic Exposure Surveillance System (TESS), exposure data from poison control

centers, overdose reference articles, and an abstract describing trends in acute liver failure in the United States.

- For aspirin/NSAIDs, FDA reviews of data and articles from the medical literature.

NDAC also considered submissions and presentations from industry and individuals during the open public sessions (Refs. 4 and 5).

B. Acetaminophen

On the first day of the meeting (September 19, 2002), NDAC considered safety issues related to the use of acetaminophen, unintentional overdose, and the potential for hepatotoxicity from both OTC and prescription acetaminophen products.

1. Points for Discussion

FDA asked NDAC to discuss possible factors that might contribute to unintentional overdose (Ref. 3) and provided the following points for consideration:

- Acetaminophen is available to consumers in many OTC and prescription drug products (i.e., single ingredient and combinations with various other active ingredients).
- Consumers fail to identify acetaminophen as an ingredient in their OTC and prescription drug products.
- Consumers are unaware of the risks of exceeding the recommended dose of acetaminophen with a single product, or of simultaneously using multiple products containing acetaminophen.

FDA asked NDAC what additional measures could be taken to better ensure that prescribers and other people are aware of the potential risks associated with exceeding the recommended dose of prescription or OTC drug

products containing acetaminophen and with using multiple products containing acetaminophen. FDA suggested the following possible measures for OTC drug products:

- Consumer education
- Changes in labeling that identify and highlight the risks
- Packaging that may enhance appropriate use
- Consumer inserts.

For prescription products, FDA suggested:

- Unit of use packaging with labeling on each blister pack
- Physician and pharmacist education
- Publication of information in professional journals
- Consumer education
- FDA publications to identify and highlight the danger and risk
- Providing patient information leaflets and stickers when dispensing the prescription.

FDA also asked NDAC if there are identifiable factors that might make some individuals more susceptible to hepatic toxicity (e.g., underlying liver disease, malnutrition, drug interactions, and alcohol users). If subpopulations at increased risk of acetaminophen-induced hepatotoxicity could be identified, FDA asked NDAC what reasonable measures could be taken to decrease their risk. FDA suggested some possible measures:

- Adjustment of the maximum total daily dose or dosing interval
- Changes in labeling that identify the population and highlight the risks
- Additional research on specific subpopulations
- Consumer and physician education.

FDA asked NDAC whether additional studies are needed to evaluate these issues. FDA suggested a number of subjects for potential research:

- Evaluation of the effectiveness of educational programs
- Evaluation of revised labeling
- Surveillance of serious acetaminophen hepatotoxicity cases
- Enhanced collection of information when medication errors occur
- Better understanding of consumer use of these products.

2. Presentations and Submissions to NDAC

As a lead-in to the liver toxicity discussion, Dr. William Lee, of the University of Texas Southwestern Medical Center at Dallas, presented the results of acute liver failure (ALF) studies in the United States (Ref. 6). He estimated that between 1,000 and 2,000 ALF cases occur in the United States each year and are associated with high mortality. Dr. Lee conducted a retrospective analysis of 177 cases of ALF reported in the literature between 1986 and 1998. Of these, 20 percent were attributed to acetaminophen toxicity. To study ALF prospectively, Dr. Lee also formed a study group of 25 treatment centers in 1998. Details of the group's initial 308 cases are presented in table 1. Approximately 40 percent of the cases were due to acetaminophen toxicity, which was increased when compared to the rate of acetaminophen toxicity in the cohort from Dr. Lee's retrospective analysis.

TABLE 1.— STUDY GROUP SERIES OF ALF CASES (N = 308)

Case Report Data	ALF Etiology				
	Acetaminophen Induced (n=120)	Drug (Not Acetaminphen) Induced (n=40)	Indeterminate Cause (n=53)	All Other Causes (n=95)	P value
Sex (% Female)	79	73	60	72	NS*
Age (years)	36	41	38	43	0.02
Jaundice (days)	1	12	12	4	<0.001
Coma (%)	50	43	47	47	NS
Alanine aminotransferase (ALT) (International Units/ Liter (IU/L))**	4310	574	947	1060	<0.001
Bilirubin	4.3	20.2	24.5	12.6	<0.001
Transplant (%)	6	53	51	36	<0.001
Spontaneous survival (%)	68	25	17	33	<0.001

TABLE 1.— STUDY GROUP SERIES OF ALF CASES (N = 308)—Continued

Case Report Data	ALF Etiology				
	Acetaminophen Induced (n=120)	Drug (Not Acetaminphen) Induced (n=40)	Indeterminate Cause (n=53)	All Other Causes (n=95)	P value
Overall survival (%)	73	70	64	61	NS

* Not significant ** ALT (normal range 0–35 IU/L)

Of the 120 acetaminophen toxicity cases identified in Dr. Lee's series, 12 were omitted due to concomitant patient issues that would have confounded the analysis. The remaining 108 cases were analyzed and showed that alcohol use was reported in 57 percent of the cases and alcohol abuse was reported in 19 percent of the cases. Individuals in 38 percent of the cases were taking both narcotic-acetaminophen prescription products and OTC acetaminophen products at the same time, some for as long as 2 to 3 months. In 70 percent of the cases, patients ingested more than 4 grams (g) of acetaminophen per day (recommended maximum daily dose), and 32 percent of the cases reported ingestion of more than 10 g per day.

A comparison was conducted among the 108 cases of toxicity due to accidental (ingestion of drugs for pain relief, without suicidal intent) and suicidal (ingestion with admitted suicidal attempt) ingestion. The type of ingestion could not be determined in 5 cases, resulting in a comparison of 103 cases (table 2). More than half of the acetaminophen toxicity cases (57 percent) were accidental.

TABLE 2.—SUICIDAL VS. ACCIDENTAL ACETAMINOPHEN ALF CASES

	Accidental (n=59)	Suicidal (n=44)	p-value
Age	39	33	0.011
Acetaminophen total (g)	20	29	NS
Antidepressant	36%	34%	NS
Alcohol (non-abuse use)	55%	61%	NS
Double use*	24%	5%	0.02
Narcotic/acetaminophen	54%	14%	0.001
ALT (IU/L)	3,616	5,929	<0.001
Creatine	2.5	1.3	0.008

TABLE 2.—SUICIDAL VS. ACCIDENTAL ACETAMINOPHEN ALF CASES—Continued

	Accidental (n=59)	Suicidal (n=44)	p-value
Survival	71%	75%	NS

* Use of more than one acetaminophen containing product.

The incidence of use of antidepressants and alcohol was nearly identical in the accidental and suicidal groups. The accidental cases included a larger percentage of subjects who double-dosed or used a narcotic/acetaminophen combination product. Survival rates were also similar. Lee concluded that acetaminophen toxicity accounted for about a third of all deaths from ALF in this case series and appears to be a growing problem in the United States.

FDA staff presented a safety analysis of hepatotoxicity associated with acetaminophen (Ref. 7). The cases were reported as ''intentional overdose'' and ''unintentional overdose.'' The reported doses were rarely within the recommended range. Four national databases were used to estimate the occurrence of these events:

1. National Hospital Ambulatory Care Survey: Emergency Department (ED) Component—a probability survey sampling of visits made to emergency departments and short stay hospitals in the United States.

2. National Electronic Injury Surveillance System—collects information on consumer product-related injuries treated in emergency departments of 66 selected hospitals.

3. National Hospital Discharge Survey—a probability survey sampling of patient discharge records from non-Federal, short stay hospitals in the United States.

4. Multiple Cause of Death Files—a data file that contains information from death certificates.

Acetaminophen overdose (unintentional and intentional) was associated with an annual average of over 56,000 emergency department visits (1993 to

1999) and more than 26,000 hospitalizations (1990 to 1999). Between 1996 and 1998, an annual average of 458 deaths was attributed, at least in part, to acetaminophen overdose. Unintentional acetaminophen overdose was associated with an annual average of over 13,000 emergency department visits (1993 to 1999), 2,189 hospitalizations (1990 to 1999), and 100 deaths (1996 to 1998). Each event in these tallies is independent from the others. No information about associated hepatotoxicity was available for these cases. FDA reviewed the age distribution for acetaminophen overdoses. Medication use varies by age and different OTC drug products containing acetaminophen are available for different age groups. The age distribution of unintentional overdose cases varies among reporting databases and is shown in table 3. While emergency department visits are most prevalent among young people, this age group accounts for the lowest percentage of cases of mortality.

TABLE 3.—AGE DISTRIBUTION OF UNINTENTIONAL CASES

	Age (years)		
	<17	17—64	>65
Emergency department visit	74%	25%	<1%
Hospitalization	23%	70%	7%
Mortality	1%	75%	23%

Chronic liver disease has been postulated to be one of the factors that increases the risk of hepatotoxicity from acetaminophen. Using the multiple cause of death database, the presence of chronic liver disease among cases of unintentional and intentional overdose with mortality outcomes was examined (table 4).

TABLE 4.—PERCENT OF LIVER DISEASE REPORTED AMONG FATAL ACETAMINOPHEN OVERDOSE CASES, MORTALITY DATA, 1996–1998

Liver Disease Reported	Unintentional (N=235)	Intentional (N=1,010)
Chronic alcoholic	13%	1%
Other chronic liver disease	48%	8%

These findings suggest that chronic liver disease, in the presence or absence of alcohol, may be a risk factor for developing or increasing severity of hepatotoxicity among people with unintentional overdose. However, this analysis has limitations. If the presence of alcohol or alcohol use was not mentioned on the death certificate, alcohol related liver disease may be misclassified as other chronic liver disease. In addition, suicide cases may be misclassified as unintentional overdose to protect privacy.

FDA also presented an analysis of cases of hepatotoxicity associated with acetaminophen from the published literature. A MEDLINE search identified all U.S. case series containing at least 10 cases that had been published in the previous 10 years (Ref. 7). Eight case series were identified, four of which were derived exclusively from review of hospital medical charts. In two series, cases were obtained from hospitals, published cases, the FDA adverse event reporting system, and poison control center databases. One case series was from a registry of cases reported by hepatologists and other practitioners. One case series was obtained exclusively from a consortium of liver transplant centers. The number of cases per series ranged from 47 to 73. Two case series were largely pediatric, and the remaining six case series consisted of largely adult populations. Six of the case series reported gender, and in all six there was a preponderance of females. Intentionality was reported in five of the series. Table 5 shows the acetaminophen dose reported among in the unintentional overdose groups.

TABLE 5.—HEPATOTOXICITY SERIES: UNINTENTIONAL TOXICITY CASES

Case Series	Reported Daily Doses (g/day)	No. of Cases in Series	No. of Cases With Typical Daily Dose of ≤4g/day
Johnston	1.3–20	53	9
Schiodt	2–30	21	3
Zimmerman	‘‘<4’’–‘‘>15’’*	67	27
Whitcomb	3.5–25	21	None

TABLE 5.—HEPATOTOXICITY SERIES: UNINTENTIONAL TOXICITY CASES—Continued

Case Series	Reported Daily Doses (g/day)	No. of Cases in Series	No. of Cases With Typical Daily Dose of ≤4g/day
Broughan	15.9 (mean)	8	None

* Dose was reported categorically.

Nine people in the Johnston case series and three people in the Schiodt case series ingested 4 g/day or less of acetaminophen. In the Zimmerman case series, 27 people used acetaminophen at the recommended dose, while 13 people used between 4.1 and 6 g/day. In the Whitcomb case series, 3 people used acetaminophen at, or slightly above, the recommended dose (i.e., 3.5 to 5 g/day in one case and 4 to 6 g/day in two cases). In the Broughan case study, none of the people took acetaminophen at the recommended dose.

Table 6 compares the number of deaths and serious outcomes for the unintentional and intentional groups. Intentionality could only be compared in the adult case series. Serious outcomes were defined as hepatic coma, acute liver failure, and liver transplant.

TABLE 6.—COMPARISON OF UNINTENTIONAL AND INTENTIONAL TOXICITY GROUPS: CASES OF DEATH OR SERIOUS OUTCOME

Case Series	Unintentional	Intentional
Johnston	17 / 53	NA*
Schiodt	11 / 21	4 / 50
Zimmerman	13 / 67	NA*
Whitcomb	5 / 21	NR**
Broughan	2 / 8	0 / 40

*NA: Not applicable; **NR: Not reported

FDA also presented case data from the TESS of the American Association of Poison Control Centers (AAPCC). At that time, AAPCC had a repository of over 27 million human poison exposures reported by over 60 participating centers. These centers covered over 90 percent of the U.S. population. Examination of AAPCC's annual reports from 1995 to 1999 of cases listing acetaminophen as the primary (first) agent showed acetaminophen to be the leading cause of poisonings. In 1999, acetaminophen-related calls represented

10 percent of all calls to AAPCC. There was a decrease in calls between 1995 (111,175) and 1999 (108,102). In 1999, nearly 50 percent of the poison victims associated with the calls received treatment in health care facilities. Two percent of these victims were reported to have developed major effects resulting from the poisoning, i.e., the signs or symptoms occurring as a result of acetaminophen exposure were life-threatening or resulted in significant residual disability. Fifty percent of the calls involved children and adolescents (19 years of age or under). Of the acetaminophen related calls regarding children under 6 years of age (approximately 40,000 calls), 22 percent occurred in children who ingested adult formulations of acetaminophen.

In 1995, there were at least 76 acetaminophen-related fatalities. By 1999, the number of acetaminophen-related fatalities increased to 141. Of these, 92 (65 percent) were a result of suicidal intent, 43 (30 percent) were unintentional, and the dosing intent for 6 (4 percent) was undetermined. Among the 43 unintentional fatalities, 28 (65 percent) took one OTC drug product containing only acetaminophen; 4 (9 percent) took one prescription product containing acetaminophen, and 11 (26 percent) took more than one acetaminophen product simultaneously. These AAPCC data may underreport the actual number of acetaminophen toxicity cases, because serious cases that go directly to emergency departments, and chronic users of acetaminophen, are unlikely to generate poison control center contacts.

FDA staff reviewed spontaneous reports of hepatoxicity in FDA's adverse event reporting system (AERS). U.S. cases were identified that had been received by FDA between January 1998 and July 2001 and in which one or more acetaminophen containing products had been ingested. Of 633 reports, 43 were duplicates. Another 283 were excluded for various reasons, primarily

to exclude cases in which there was apparent suicidal intent. A total of 307 cases were included in FDA's analysis (25 pediatric and 282 adult cases).

Pediatric cases (of children age 1 day to 8 years) consisted primarily of males (approximately 70 percent), although gender was not reported in each case. Fifteen of the 25 pediatric cases involved severe, life-threatening liver injury. Of the 25 children, 10 died, 21 were hospitalized, and 2 required only treatment in an emergency department. The dose was estimated, based upon reported daily doses and weight, in 10 cases to be 106 to 375 milligrams/ kilogram (mg/kg) per day. The recommended pediatric dose is 75 mg/kg/day (Ref. 7). Twenty-two of the children (88 percent) took only 1 product containing acetaminophen and 3 children (12 percent) took 2 or more products containing acetaminophen. Sixteen of the cases (53 percent) reported ingestion of a single ingredient acetaminophen product (APAP), 12 cases (40 percent) reported ingestion of an ''unspecified APAP product'' and the remainder of the cases reported ingestion of combination products. Of the single ingredient products, concentrated drops containing acetaminophen 100 mg/milliliter (mL) were reportedly ingested in seven cases.

In 20 of the pediatric cases, 1 or more medication errors were reported. In three cases, the wrong product was used, i.e., the concentrated drops instead of the children's acetaminophen liquid formulation. In four cases, incorrect measuring devices were used, i.e., teaspoonfuls instead of dropperfuls. Five cases reported instances of misinterpretation of labeled dosing guidelines or misinterpretation of instructions provided by a health care provider.

Sixty percent of the 282 adult cases (15 to 85 years old) were female and 229 required hospitalization. A total of 169 adults experienced severe, life-threatening liver injury; 124 of these patients died and 7 required a liver

transplant. One hundred ninety-nine (71 percent) adults reported using an acetaminophen product for a therapeutic indication, primarily analgesia. In 74 (26 percent) cases, the indication for use was unknown, and in 9 (3 percent) cases, abuse of a narcotic-acetaminophen prescription product was reported. One hundred thirty-eight (38 percent) cases listed an unspecified acetaminophen product (unknown whether single ingredient or combination product and whether OTC or prescription), 122 (33 percent) cases involved the use of a narcotic-acetaminophen prescription product, and 76 (21 percent) cases reported use of an OTC single ingredient acetaminophen product. Approximately 25 percent of all adult cases reported use of more than one acetaminophen product. When more than one acetaminophen product was reported, a narcotic-acetaminophen prescription product in combination with an OTC product containing acetaminophen was used more often than any other combination of acetaminophen products. These cases also used higher doses than people who took only one acetaminophen-containing product.

Dosing amounts were reported in 132 of the 282 adult cases. The mean and median daily dose were 6.5 and 5 g, respectively, but ranged from 650 mg to 30 g/day. Where the dosage strength was known, 500 mg acetaminophen was reported most often. If a dose range was reported in the case, the mid-point was used in the analysis. If the strength was unknown, a 500-mg strength was assumed. Dosing in the 65 adults with severe liver injury from this group showed a mean and median daily dose of 7.1 and 6.23 g, respectively. Twenty-three of the 65 cases with severe liver injury reported doses of less than 4 g/day. People who used more than one acetaminophen product reported taking higher doses than people who took a single product. Qualitative dosing information was provided for an additional 43 (15 percent) cases with terms

such as ''excessive doses'' or ''recommended doses.'' Two out of three of these cases suggest that greater than recommended doses were used.

Alcohol use was reported in 116 of the adult cases and the content of the reports was highly variable. Alcohol use in these cases was defined by FDA as alcoholism or alcohol abuse in 64 cases; regular, daily, or moderate use in 23 cases; occasional use in 10 cases; previous use in 6 cases; and 13 cases did not provide a description. Eighty-six (74 percent) of the 116 alcohol users developed severe liver injury. For those cases with acetaminophen dose information, the mean dose associated with toxicity was lower for alcohol users compared to nonalcohol users (table 7).

TABLE 7.—ACETAMINOPHEN DOSE AND ALCOHOL USE

Category of Liver Disease (Developed Post-Acetaminophen)	Alcohol Users (Mean Dose)	Non-Users (Mean Dose)
All (N=132)	5.6 g (N=53)	6.9 g (N=79)
Severe only (N=65)	6.0 g (N=38)	8.6 g (N=27)

A history of prior liver disease, or possible underlying liver disease, was reported in 70 cases. In at least 20 of these cases, the pre-existing liver disease was reportedly due to alcohol. Twenty-three people reported a history of, or possible, viral hepatitis. Among the 70 cases with pre-existing liver disease, 49 percent (70 percent) developed severe liver injury. Table 8 shows the dose that was associated with liver injury for cases with and without pre-existing liver disease. The first row includes all cases (all degrees of acute liver injury) that reported dosing information. The second row shows a dose comparison in people who experienced severe liver injury after acetaminophen exposure.

TABLE 8.—ACETAMINOPHEN DOSE AND LIVER DISEASE

Category of Liver Injury Associated With Acetaminophen Dosing	Cases With Pre-existing Liver Disease (Mean Dose)	Cases With No Pre-existing Liver Disease (Mean Dose)
All (N=132)	5.4 g (N=36)	6.8 g (N=96)
Severe only (N=65)	5.7 g (N=23)	7.8 g (N=42)

Some additional factors may have contributed to the development of hepatotoxicity in these adults. Use of other medications that may have contributed to hepatotoxicity was reported in 93 cases, including 63 cases that involved products that are labeled with warnings about potential hepatotoxicity. A small number of reports also mentioned the existence of concomitant malnutrition or decreased oral intake.

FDA noted that there are limitations to interpreting the AERS data. Dosing information may be unreliable. Acetaminophen products are generally taken on an as-needed basis, so the actual dose ingested can be difficult to ascertain. There is no certainty that all of the adult cases included in this analysis were unintentional. Stigma may be associated with reporting suicide, so cases may be reported as unintentional when they were intentional overdoses. In addition, spontaneous reporting systems cannot provide certainty that acetaminophen was the cause of any of the reported adverse event. Furthermore, incidence rates cannot be determined, because the numerator or denominator descriptors for the entire population are not available. Overall, spontaneous reports may be subject to significant underreporting.

The AERS cases strongly suggest that particular circumstances were likely to have led to hepatotoxicity. Some examples of those circumstances follow:

- Errors related to product confusion were mostly observed in pediatric cases. These errors primarily involved confusion over varying product formulations and strengths and use of inappropriate measuring devices.
- Many adults were taking more than the recommended dose of acetaminophen and, in some cases, use of multiple products likely contributed to hepatotoxicity.

- Risk factors, such as alcohol use or pre-existing liver disease, were identified and may have increased the risk for hepatotoxicity.

FDA presented NDAC with several questions that remained unaddressed by FDA's review:

- Do users lack knowledge of the potential for and symptoms of hepatotoxicity when using a product containing acetaminophen?
- Does malnutrition or fasting affect severity of hepatoxicity?
- What is the contribution of concomitant hepatotoxic medication?
- What additional factors place a small number of individuals at risk for severe hepatotoxicity at various dose levels (i.e., under, at, or above the recommended dose)?

It is clear that unintentional acetaminophen doses are associated with a large number of emergency department and hospital admissions and are related to an estimated 100 deaths each year. Using a number of data sources, analyses have shown that circumstances leading to acetaminophen hepatotoxicity are multifactorial. FDA asked the committee to consider the contribution of each of the following in producing unintentional overdose toxicity:

- *Product*—the ingredient is present in multiple prescription and OTC drug products and in multiple oral formulation strengths
- *Knowledge*—since a number of cases have occurred from multiple product use and overuse, there is likely a lack of knowledge about safe use of acetaminophen
- *Risk factors*—multiple data sources identify alcohol and underlying liver disease as risk factors that may increase the potential for hepatotoxicity.

Several drug manufacturers and other interested parties provided additional comment (Ref. 4):

- One major manufacturer of acetaminophen OTC drug products provided the following comments:

1. The precise incidence of harmful, unintentional overuse cannot be accurately determined from the current databases. Forty-eight million American adults use products containing acetaminophen in any single week; thus, harm is rare and is caused by inadvertent overdose.

2. There are limitations to the AERS data set for assessing hepatic events. Patients consistently underestimate the dose taken, and suicide attempts are often not recorded in patients who are found unconscious or intoxicated. The AERS reports found to be definitely associated with acetaminophen involved substantial overdose in individuals with self-abusive behaviors (e.g., alcohol abuse, bulimia). Causality cannot be ascertained using retrospective data, especially case reports, because the dose history is often inaccurate.

3. Formulations most commonly reported were OTC single-ingredient and prescription combination acetaminophen products. OTC acetaminophen combination products were rarely reported.

4. Serious hepatotoxicity occurs following substantial overdose (a single dose of approximately 15 g or use of approximately 12 g for multiple days).

5. FDA focused on unintentional misuse. The manufacturer noted they had implemented labeling changes to minimize the inadvertent overuse of analgesics. The manufacturer recommended an organ specific overdose warning.

- One manufacturer of ibuprofen OTC drug products provided the following comments:

1. In overdose situations, in any given year, the number of deaths for acetaminophen reported by the AAPCC is approximately 20 times that for ibuprofen.

2 . Unintentional overdose of acetaminophen can put consumers in a life-threatening situation due to the delayed onset of clinical symptoms of toxicity.

3. Advertising portrays acetaminophen as a totally safe ingredient. This portrayal may exacerbate use and contribute to the silent danger resulting from overdose.

- One individual presented a review of acetaminophen overdose admissions at the University of Pennsylvania hospital over a 4-year period. Fifty-four reports of acetaminophen overdose were found in the hospital's database. Of the 47 cases reviewed to date, 23 (50 percent) were reported to be unintentional overdoses. In 13 of these 23 cases, the reviewer was able to document that an attending physician or a psychiatry consultant concluded that there had been no suicidal intent.

1. The median and average doses were between 6 and 8 g/day. These values are above the recommended maximum daily dose (4 g/day), but below the 10 to 15 g dosage usually considered to be toxic. There were three cases of intentional overdose and three cases of unintentional overdose involving prescription acetaminophen products. OTC products were associated with 20 intentional and 21 unintentional overdoses. More patients in the unintentional overdose group used single ingredient acetaminophen (i.e., not a combination product). The primary reason reported for exceeding the maximum dose was to treat unrelieved pain. Many patients stated that they knew they were exceeding the recommended dose and did so because they thought it was a

safe drug. Thirty percent of the patients used the drug over a period of greater than 7 days.

2. The unintentional overdose group experienced greater morbidity and mortality than the intentional overdose group. The peak acetaminophen levels in the intentional overdose group were much lower compared to the unintentional overdose group (27.8 versus 115.1 mg/L). The unintentional overdose group had much higher peak levels of Alanine aminotransferase (ALT) (5,193 versus 3,065 units/L), Aspartate aminotransferase (AST) (6,819 versus 2,742 units/L), International Normalized Ratio (INR) (4 versus 2.5), and total bilirubin (5.87 versus 1.87 mg/dL). Patient outcomes were generally worse in the unintentional overdose group, in which more patients failed to have resolution of the liver problems from the overdose (31 versus 4 percent). More patients were evaluated for transplants (11 versus 9), received transplants (2 versus 0), and died (3 versus 0) as a result of unintentional overdoses.

3. Compared to the intentional overdose group, the unintentional overdose group was more likely to have one or more of the following risk factors for acetaminophen toxicity: (1) Hepatic disease, (2) acute or chronic alcohol use, (3) drug abuse, or (4) concomitant disease. Ninety-six percent of cases in the unintentional overdose group had one or more of these risk factors, as compared to 70 percent in the intentional group. Acute and chronic alcohol use was present in 87 percent of unintentional overdose cases, as compared to 61 percent of the intentional overdose cases. Thus, the existence of risk factors may have an impact on toxicity in unintentional ingestions.

- One individual described the untimely death of her son who initially used a prescription product. When the prescription was finished, he purchased an OTC acetaminophen product and developed flu like symptoms. Another

OTC acetaminophen product was subsequently used to treat the flu symptoms, resulting in hepatotoxicity. He was hospitalized and ultimately died.

- A professional pharmaceutical association encouraged consumers to carefully read product labeling. The association also recommended: (1) Clear labeling on all prescription and OTC drug products containing acetaminophen with special statements (e.g., ''contains acetaminophen'' on the product's PDP), and (2) pharmacists placing auxiliary labels on the vial of prescription drug products containing acetaminophen to identify this ingredient.

- A consumer public health organization described a consumer survey showing that many consumers do not recognize the potential for harm from: (1) Taking more than the recommended dose, (2) taking more than one product containing acetaminophen, or (3) inappropriately combining OTC and prescription drug products containing acetaminophen.

- A member of a national health foundation expressed concern that present marketing practices make it very difficult to find the standard 325-mg acetaminophen dosage unit. As a result, many consumers believe that the 500-mg product is the only one available. This failure to more broadly market the lower dose may contribute to increased adverse events. The individual advocated educational efforts to help minimize this problem.

- A spokesperson for a national consumer organization described marketing limitations that are employed in the United Kingdom and intended to limit the potential for overdose. In September 1998, a restriction was placed on the number of tablets in acetaminophen packages for sale without a prescription. If sold in a supermarket, the maximum is 16 tablets per package. If sold in a pharmacy, the maximum is 32 tablets per package. There is also an overall restriction that a maximum of 100 tablets can be purchased at one

time. The representative stated that early evaluations of this program have shown decreases in (1) total and severe acetaminophen overdoses and (2) overdoses related to liver transplant and death.

Several drug manufacturers and others submitted additional information for the committee to review (Ref. 5):

- One major manufacturer of acetaminophen OTC drug products provided the following comments (Ref. 5, Tab A):

1. AERS serves as a signal generating system for rare, unexpected adverse events in marketed products. It cannot be used to determine event rates, dose ingested, or patient dosing intent.

2. FDA's review of the AERS data set was intended to exclude obvious suicide, usually associated with very large drug ingestion. Thus, the reported dosage (which could only be estimated in 48 percent of the reports in the data set) is skewed significantly toward labeled directions for use, so cases may falsely appear to be consistent with inadvertent misuse.

3. The selective data in FDA's AERS review cannot be used to determine an acetaminophen toxicity threshold associated with any patient condition (i.e., concomitant drug, alcohol history, or pre-existing concomitant disease).

4. The quality of the 281 adult reports in AERS was evaluated by the manufacturer. The manufacturer concluded that 168 reports (24 percent) contained insufficient information to estimate the dose taken and 212 reports (88 percent) contained no liver pathology information. AST and ALT levels were not reported in 108 cases (38 percent). Only 61 reports (25 percent) had information about viral hepatitis testing and, of these, 29 reports were positive for hepatitis A, B, or C.

5. There are flaws in the derivation of FDA's theory that alcohol use, underlying/history of liver disease, and potentially the use of hepatotoxic concomitant medications, may increase susceptibility to acetaminophen-associated hepatotoxicity at unexpectedly low doses of acetaminophen. The manufacturer provided arguments that the existence of any of these factors in a case report may each inherently interfere, for various reasons, with establishing the correct assessment of a hepatotoxic dose of acetaminophen.

- An expert panel sponsored by a manufacturer of acetaminophen products reviewed all 281 adult reports in AERS and assigned a probability category relating the reported hepatic adverse events to acetaminophen exposure. In 3 reports the adverse event and exposure were considered ''definitely'' related, in 74 reports they were ''probably'' related, 47 reports they were ''possibly'' related, in 53 reports they were unlikely to be related, and in 27 reports they were definitely not related. Data were considered insufficient in 73 reports, 3 reports were not able to be evaluated and there was no consensus regarding the evaluation of 1 report.

Based on an assessment of several databases, a sponsor calculated that the worst case scenario of deaths from acetaminophen overdose is estimated to be 213 deaths per year (Ref. 5, Tab A).

- One manufacturer submitted an analysis of data from TESS (Ref. 5, Tab B). The manufacturer made the following conclusions from these data:

1. The majority of hepatotoxicity cases (65 percent of cases in the year 2000) involved use of one acetaminophen-containing analgesic product.

2. Acetaminophen-containing cough/cold medications were not a significant contributor to the total number of reports of acetaminophen associated hepatotoxicity (2 percent of cases in the year 2000).

3. Only 1 percent of the reported cases of hepatotoxicity in 2000 involved use of an OTC acetaminophen-containing cough/cold product concomitantly with other acetaminophen-containing product(s).

- One physician stated that 3 to 4 g of acetaminophen per day is the upper range of a safe dose (Ref. 5 Tab C). For an individual who is a regular user of alcohol, in a prolonged fasting or in a rapid weight loss program, the upper limit of a safe dose is unknown, but unlikely to not exceed 2 g of acetaminophen. No data were provided to support these observations.
- Several organizations urged that labeling be improved to provide clear directions about the appropriate doses for use and frequency of administration, especially for combination products (Ref. 5 Tab D). Consumers need to know the type of medication and the dose of OTC analgesic in every combination product to ensure safe and effective use.

3. NDAC Deliberations and Recommendations Concerning Acetaminophen

NDAC unanimously agreed that the evidence of risk associated with unintentional overdose of acetaminophen warrants FDA labeling changes, without awaiting the outcome of further studies. NDAC noted the following four major areas of concern:

1. Unintentional use of multiple acetaminophen containing products
2. Exceeding the recommended dose without recognizing the consequences
3. Improper dosing of infants
4. The unknown consequences of use in special populations, such as alcohol abusers.

NDAC recommended that the minimum requirements for change should include, for all products containing acetaminophen (including those available

by prescription), the addition of distinctive labeling (highlighted or bold type) on the front panel or PDP to state that the products contain acetaminophen. FDA noted that the nonproprietary name of prescription drugs must appear in labeling in letters at least half the size of the brand name (see 21 CFR 201.10(g)(2)). NDAC recommended that a similar provision also be applied to OTC drug products containing acetaminophen, such as a standard to ensure prominence of important information. NDAC stated that consumers need to be informed that combining products containing acetaminophen can result in exceeding the recommended dose.

NDAC commented that there are insufficient data in the OTC setting on risk management, understanding consumer behavior, and the effectiveness of warnings on labels. This lack of data makes it difficult to determine which factors contribute to liver injury. Although these factors are not clearly understood, NDAC concluded that labeling revisions are needed to help minimize any risks.

- *Separate liver toxicity and alcohol warnings*. NDAC recommended a liver toxicity statement, separate from the alcohol warning, be added to the label so that the potential for liver toxicity would not appear to be applicable only to consumers who drink alcohol. NDAC noted that alcohol is not the only risk factor for hepatotoxicity. It was also felt to be important to warn consumers of the consequences of taking multiple products containing acetaminophen and that toxicity can be related to the total dose of acetaminophen taken during a given period of time. NDAC felt it would be more prudent to describe these risks in a separate warning to more fully inform consumers who do not abuse alcohol.

NDAC did not propose exact language. It was believed that it was important that the message not refer to ''overdose,'' but rather to a statement such as ''do not take more'' or ''do not exceed the recommended dose.'' NDAC believed that the term ''overdose'' would not be understood to be pertinent to consumers whose intent was to use the product safely. One NDAC member stated the term ''exceed'' is not part of consumers' common vocabulary and proposed that it would be more useful to inform consumers of a specific allowable total dose (e.g., not to take more than a specified number of tablets in a given period).

NDAC re-examined the currently required alcohol warning for acetaminophen, which states: ''Alcohol Warning: 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.'' NDAC inquired why ''three drinks'' were used in the alcohol warning. FDA responded that the number is from recommendations of the American Heart Association as to what constitutes excessive alcohol use. FDA stated that it recognized this may seem arbitrary and asked NDAC to provide further recommendations. NDAC questioned whether doctors are well-informed with proper information about the relationship between alcohol and acetaminophen use and whether educational efforts should also include educational efforts directed at health care professionals and consumers. NDAC was concerned about the lack of available data on which to base such advice, noting that there is a lack of information about how to determine the amount of alcohol that may be harmful to any individual. NDAC noted that reducing the risk of drug adverse events is the goal, but believed that more data are essential for them to make specific recommendations.

FDA asked NDAC to comment on whether the current maximum allowable daily dose of acetaminophen should be used by individuals consuming three or more drinks per day. One NDAC member agreed that was prudent to lower the dose, however, the majority of NDAC members believed that more information is needed before dose reductions could be implemented for this population. NDAC stated that, intuitively, a lower dose would decrease potential toxicity, but noted that there is a lack of information to support such labeling.

One NDAC member mentioned that although some evidence appeared to show an association of increased acetaminophen toxicity for patients with pre-existing liver disease, this finding is contrary to hepatologists' experience with acetaminophen. Generally, acetaminophen is considered safe for use in patients with liver disease, including people awaiting liver transplantation. Most hepatologists recommend acetaminophen for such patients, but at reduced doses, such as 2 g maximum in a 24-hour period. NDAC urged more studies, not only of risk factors, but of a plan to reduce risk.

- *Consumer and healthcare provider education*. NDAC concluded that FDA and manufacturers have a joint responsibility to reduce the occurrence of unintentional overdoses from acetaminophen. NDAC considered it essential that consumer and professional educational programs heighten awareness of the risk, particularly to certain populations. NDAC believed consumers are unfamiliar with the term ''acetaminophen'' and are more likely to know the brand names. NDAC stated that an effort should be made to create a broader educational campaign to inform consumers that acetaminophen is an analgesic, because most people are familiar with aspirin and not with acetaminophen. NDAC also suggested that the packaging, display, format, and wording

recommendations in OTC drug product labeling should also be extended to all product advertisements, both in print and media, because advertising is an educational tool for many consumers.

NDAC stated that many physicians and pharmacists may not be aware of the risks of unintentional overdose. NDAC added that, along with consumer education, professional programs are important, because prescription products containing acetaminophen are widely used. Education of pharmacists would be needed to support the use of additional labeling information (stick-on labels, etc.) attached to prescription containers. NDAC stated that auxiliary labeling is critical to conveying information that the prescription product contains acetaminophen.

- *Pediatric dosage*. NDAC also expressed concern about the lack of standardized pediatric dosage information, especially for infants under 2 years of age. FDA stated that a separate rulemaking on this issue was in progress and will be addressed in a future **Federal Register** publication.

C. Aspirin and Other NSAIDs

On the second day of the meeting (September 20, 2002), NDAC considered safety issues related to the use of aspirin and other OTC NSAIDs. The primary areas for discussion included the potential for GI bleeding and renal toxicity from using these drugs. The prescription labeling for NSAIDs and the professional labeling for aspirin have warnings for GI bleeding and possible renal toxicity. Aside from the alcohol warning required on all OTC NSAID drug products, current OTC labeling does not have warnings about damage to specific organs.

1. Points for Discussion

FDA asked NDAC to consider the relative risks for GI bleeding and renal toxicity associated with OTC doses of NSAIDs, including aspirin, and to consider the following issues:

- How should the relative risk of GI bleeding or renal toxicity be described to consumers who use the maximum recommended daily OTC dose?
- Are there subpopulations of consumers who are at a greater risk for developing GI bleeding or renal toxicity with OTC doses?
- If additional warnings are recommended, should such warnings inform consumers about the risk, provide information on the at-risk populations, or provide expanded information to all consumers about symptoms of toxicity?
- Should the warnings that are currently in professional labeling for aspirin be conveyed to consumers as part of the OTC labeling?
- If yes, which warnings should be conveyed and how should they appear in OTC drug product labeling?
- Are any additional studies needed to evaluate subpopulations at risk for serious adverse events, labeling revisions, and any other issues?
- Should the labeling and packaging of these products more prominently state that the product contains aspirin or the specific NSAID?

2. Presentations and Submissions to NDAC

GI bleeding

FDA staff described cases of GI bleeding (spontaneous reports from AERS received by FDA between 1998 and 2001) in individuals who used OTC NSAIDS (including aspirin) as an analgesic and/or antipyretic (Ref. 8). The review was limited to cases that mentioned ''OTC'' in the narrative of the report. Any cases that appeared to involve prescription NSAID products were

excluded. A total of 279 cases of GI bleeding were included: 82 for aspirin and 197 for nonaspirin NSAIDs (i.e., ibuprofen, ketoprofen, and naproxen). The mean age was 59 years (ranging from 1 to 99 years). There were 138 (49.5 percent) males, 119 (42.7 percent) females, and 22 cases (7.9 percent) in which gender was not reported.

Cases that specified the location in the GI tract of the bleed included: Stomach (63 cases), duodenum (35 cases), unspecified upper GI site (15 cases), esophagus (13 cases), and rectum/colon/small intestine (9 cases). For nonaspirin NSAIDs, the median time to onset was 7 days. Time to onset was defined as the time between each person's first use of the drug and the time that bleeding occurred. For aspirin, time to onset was about 30 days. For both aspirin and nonaspirin NSAIDs, there was a wide range in time to onset. FDA reviewed the cases for common risk factors for GI bleeding that are recognized in the medical literature, including previous GI bleed or history of an ulcer, social history (alcohol or tobacco use), concomitant use of other drugs (NSAIDs, aspirin, anticoagulants, corticosteroids), use of doses higher than recommended, and advanced age (65 years and older). The results included 195 (70 percent) cases with at least one risk factor, 112 (40 percent) cases with more than one risk factor, and 81 (29 percent) cases with no risk factors apparent in the report. The most commonly reported risk factors were:

- Concomitant use of another NSAID or aspirin (50 percent)
- Advanced age (40 percent)
- History of a previous GI bleed (18 percent)
- Using NSAID doses above the recommended OTC dose (14 percent)
- Alcohol or tobacco use (5 percent).

In the aspirin cases, only one person was reported to have exceeded the OTC recommended dose. Of the 279 aspirin and nonaspirin cases, 212 people (76 percent) were hospitalized. Most recovered; however, 13 (4.7 percent) people died.

FDA indicated that these reports suggest that serious GI bleeding events can occur with NSAID and aspirin use at OTC dosage strengths, within the duration of use described in the OTC labeling.

Dr. Byron Cryer, of the University of Texas Southwestern Medical School, provided an overview of the GI risks from NSAID use (Ref. 9). His review was not limited to OTC dosing of NSAIDs and extended to all NSAIDs. He made the following points:

- Despite the overall decrease in prevalence of uncomplicated ulceration, the incidence of complicated ulcerations (specifically, bleeding ulcers) has increased in the past few years. This is likely due to increased NSAID exposure, possibly from OTC use. Gastric ulceration (15 percent prevalence) associated with NSAIDs (at recommended doses) is much more common than duodenal ulceration (5 percent prevalence). Clinically relevant ulceration (i.e., ulcers that present with bleeding), has a prevalence of approximately 2 percent.

- A history of prior bleeding, anticoagulant use, corticosteroid use, and increasing age are factors that increase the risk of bleeding associated with NSAIDs (Refs. 10 through 13).

- The prevalence of upper GI bleeding from aspirin use is different than for nonaspirin NSAID use. A study evaluated the prevalence of aspirin and nonaspirin NSAID use in 421 patients evaluated for upper GI bleeding (Ref. 14). Patients were asked at the time of hospital admission whether they were using prescription or OTC products and whether they were using nonaspirin

NSAIDs or aspirin. The results show that 42 percent of GI bleeding was associated with aspirin use. Fourteen percent of patients admitted to the hospital were using prescription NSAIDs and 9 percent were using OTC NSAIDs.

- A recent study suggests that up to 80 percent of people with GI bleeding are taking an NSAID, primarily low dose aspirin (Ref. 15). The relative risk (RR) (i.e., the probability of an event in the active group divided by the probability of the event in the control group) was 2.4 for a low/medium NSAID dose and 4.9 for a high dose.

- Another study compared the use of OTC aspirin, ibuprofen, naproxen, and acetaminophen between two case groups, one group who experienced GI bleeding events and a control group of cases who did not experience GI bleeding (Ref 16). The patients in the GI bleeding group were more likely to be taking aspirin or OTC NSAIDs prior to the GI bleeding event than were patients in the control group. The extent of use of acetaminophen was comparable between the two groups. This study included people with chronic disease and chronic analgesic exposure, providing information about a subgroup of patients that may be different from relatively healthy individuals exposed to OTC analgesics for acute, short-term, or intermittent use.

- The risk of combining low dose aspirin with nonaspirin NSAIDs was examined in a large national cohort study in Denmark (Ref. 17) in which 27,000 people were given 100 to 150 mg aspirin every day. The study showed that there is an increased risk of upper GI bleeding in patients who combine low dose aspirin and other NSAIDs compared to the incidence of GI bleeding events in the general population (RR 5.6; 95% confidence interval (CI) 4.4—

7.0). The risk of GI bleeding among patients taking more than one NSAID was approximately double the risk among patients taking aspirin alone.

- In an American College of Gastroenterology Bleeding Registry (Ref. 18), cases of GI bleeding were assessed for use of aspirin or OTC NSAIDs and concomitant use of alcohol. These cases were compared to data from a control cohort of cases with no GI bleeding. The results suggest an increased risk of bleeding when alcohol is used while taking an OTC NSAID (odds ratio 4.47; 95 percent CI 2.73 -7.32) compared to the use of either alcohol or OTC NSAIDs alone (odds ratio for alcohol alone 2.07; 95 percent CI 1.48—2.88/ odds ratio for NSAID alone 2.76; 95 percent CI 2.03—3.74). Dr. Cryer noted that the results of the study were confounded because 12 percent of the subjects in the registry had gastric or esophageal varices (enlarged veins). He suggested that there may be an increased risk particularly to patients with an extensive history of alcohol use who are exposed to OTC NSAIDs.

- Another report (Ref. 19) evaluated subjects who regularly or occasionally used aspirin or ibuprofen and compared the RR of GI bleeding between those who never used alcohol and those who used alcohol. The results suggest a modest increase in RR of upper GI bleeding in alcohol users; however, the statistical analyses did not provide a strong distinction between alcohol users and non-users.

Dr. Marie Griffin of Vanderbilt University discussed additional information obtained from large population studies regarding GI complications associated with the use of NSAIDs (Ref. 20). She made the following points:

- The risk of ulcer disease was shown to increase 10-fold in older people and this risk is increased further by use of NSAIDs (Ref. 21). This ulcer hospitalization study found the absolute risks to increase from approximately

4 hospitalizations per 1,000 person-years in older non-users of NSAIDs to approximately 16 hospitalizations per 1,000 person-years in older users of NSAIDs. In general, consumers taking NSAIDs for a year at moderate doses have about a 1 to 2 percent chance of being hospitalized with a complication.

- The risk of hospitalization for peptic ulcer disease (PUD), and risk of GI complications, increases with increasing NSAID doses (Refs. 20, 22, and 23).

- Data obtained from the Tennessee Medicaid database indicate that the greatest absolute risk for hospitalization for PUD occurs in the first 30 days of NSAID use among patients older than 65 years of age (Ref. 23). For older patients, there were 26.3 hospitalizations for PUD per 1,000 NSAID users per year within 30 days of starting NSAID therapy, 20.9 hospitalizations between 31 and 180 days of use, and 16.2 hospitalizations for use longer than 180 days. In contrast, there were 4.2 hospitalizations per 1,000 NSAID non-users per year. Overall, people of all ages have a 1 to 2 percent chance of being hospitalized with a complication when using NSAIDs for over a year at moderate doses.

- Surveys in the 1980s showed that approximately 1 to 3 percent of people 65 and older take a prescription corticosteroid drug. The concomitant use of an OTC NSAID with a corticosteroid increases the risk of ulcer complication 13- to 15-fold over NSAID non-users. The ulcer hospitalization rate in people using both drugs was about 5 to 6 per 100 people per year.

- In the 1980s, 1 to 2 percent of the elderly population were co-prescribed warfarin (an anticoagulant drug) and NSAIDs. The risk of GI bleeding increased by 12 fold in patients who used both therapies compared to NSAID non-users.

The risk of hospitalization for GI bleeding is approximately 3 per 100 per year in patients who use warfarin and NSAIDs.

Several drug manufacturers and others provided additional comments (Ref. 4):

- One drug manufacturer of ibuprofen OTC drug products stated that the OTC ibuprofen daily regimen is 1,200 mg/day versus 2,400 to 3,200 mg a day for prescription use. Unlike acetaminophen, the OTC directions clearly state to take one 200-mg tablet and, only if necessary, a second tablet may be taken. OTC use of NSAIDs is limited to a maximum of 10 days, whereas prescription use is chronic.

- One drug manufacturer stated that each analgesic ingredient requires appropriate labeling for its pattern of use and that it is inappropriate to label OTC products with risks associated with chronic, long-term prescription dosing. The prescription and OTC uses of NSAIDs are distinct and these two dose levels have different risk-benefit profiles. The OTC use is short-term for pain relief and fever reduction, with a low risk. Results of prevention studies of secondary and acute myocardial infarction have shown that for people whose 10-year risk of having a subsequent cardiovascular event is between 20 and 50 percent, the cardiovascular benefit of aspirin far outweighs the risks. The relative and absolute risks of aspirin are low.

- One consumer advocacy organization stated that GI bleeding caused by NSAIDs (reference to prescription or OTC products was not specified) is now recognized as the most common serious adverse drug reaction in the United States and accounts for as many as 16,000 deaths a year. The organization requested that: (1) Product labeling contain a clear organ-specific warning about GI bleeding, (2) packaging include consumer education on GI bleeding,

such as a leaflet inside the packaging listing specific symptoms and factors associated with increased risk, and (3) a separate warning, about increased risk of GI bleeding associated with alcohol use, be added and directed at consumers who drink some alcohol.

Several drug manufacturers submitted additional information (Ref. 5):

- One manufacturer stated that the safety profile for OTC ibuprofen, generated over 18 years of OTC use by millions of consumers, indicates that the current labeling has been effective in informing consumers of the appropriate use of the drug (Ref. 5, Tab E). The manufacturer stated that FDA has received an average of 18 reports per year of GI perforations, ulcers, or hemorrhage associated with OTC use.

- One manufacturer stated that no antidote is available for aspirin or ibuprofen overdose (Ref. 5 Tab F). Acute overdose and chronic aspirin toxicity are associated with significant morbidity (as high as 25 percent). If acetaminophen was restricted, aspirin and other NSAID use would increase. Available data suggest that more people would die from aspirin and other NSAID-related GI bleeding. The net public health impact of changing labeling for OTC IAAA drug products should be taken into consideration in the formulation of any regulatory policy.

- One manufacturer stated that the risk patterns associated with use of acetaminophen and aspirin are distinct from one another and support different product labeling for the various ingredients in OTC IAAA drug products (Ref. 5, Tab G). There are no data to support the view that a balanced warning for acetaminophen will cause a significant number of patients to switch to another OTC analgesic. Available data indicate that both the absolute number, and the rate (per billion tablets sold), of fatalities associated with acetaminophen

overdose in the United States significantly exceeds the corresponding figures for aspirin overdose.

- One manufacturer stated that the occurrence of GI adverse events with naproxen/naproxen sodium at single low dose (220 mg), at multiple doses (up to 880 mg), and as needed OTC doses, are comparable to the occurrence associated with use of placebo (Ref. 5, Tab H). Nausea, dyspepsia, and vomiting are the most common GI adverse events.

Renal effects

FDA staff presented information about the potential for OTC NSAIDs to cause nephrotoxicity (Ref. 24) and made the following points:

- NSAID-induced nephrotoxicity at prescription doses is characterized by fluid and electrolyte disturbances leading to sodium retention, edema (accumulation of watery fluid in cells and tissues), and hyperkalemia (high concentration of potassium in the blood). These drugs can also cause blood pressure to increase. The majority of healthy people who are exposed to therapeutic doses of NSAIDs for a limited time tolerate these drugs without untoward renal effects. Some subsets of the population are more susceptible to potentially life-threatening nephrotoxicity (e.g., acute renal failure and serious fluid and electrolyte disorders), including people who have volume depletion, underlying kidney disease, congestive heart failure, or liver dysfunction with ascites (accumulation of fluid in the peritoneal cavity of the abdomen), and the elderly. The use of NSAIDs in the last trimester of pregnancy has been associated with significant neonatal nephrotoxicity.

- Ideally, an assessment of the nephrotoxic risk associated with OTC NSAIDs should rely on data derived from prospective, randomized, placebo-controlled and adequately powered studies in healthy, as well as at-risk,

populations. However, such data are not available. In 1995, the National Kidney Foundation (NKF) convened a group of investigators and clinicians to consider and develop recommendations on the issue of analgesic-related kidney disease. The database used to make their recommendations was comprised of 556 articles published in the medical literature on aspirin, acetaminophen, aspirin-acetaminophen combinations, and NSAID-related nephrotoxicity. The NKF recommended ''[t]here should be an explicit label warning people taking over-the-counter NSAIDs of the potential renal risks of consuming the drugs.''

- FDA staff identified all cases in the AERS database reporting acute renal failure, chronic renal failure, and renal failure in association with the use of OTC doses of NSAIDs. The time period reviewed was from the OTC approval date for ibuprofen (1984), naproxen sodium (1994), and ketoprofen (1995) through August 10, 1999. FDA's review included cases that specified that either OTC dosages and/or an OTC NSAID product had a role in the adverse reaction. People with pre-existing conditions were not included. Table 9 shows the number of cases of renal failure reported, including 94 cases for ibuprofen, 26 cases for naproxen sodium, and 1 case for ketoprofen. Fifty-six people who used ibuprofen required hospitalization; nine needed dialysis; and nine died. Renal failure occurred within less than 7 days of exposure to the drug. Fourteen ibuprofen cases were within the pediatric age group. For naproxen sodium, 25 people were hospitalized, 4 required dialysis, and 3 died. The single ketoprofen case was hospitalized.

TABLE 9.—FDA AERS CASES OF RENAL FAILURE AT OTC DOSES OF NSAIDS

	Ibuprofen	Naproxen Sodium	Ketoprofen
Reporting Period	15 years	5 years	4 years
Renal Failure Cases—Total	94	26	1
Renal Failure Cases—Adult	80	26	1

TABLE 9.—FDA AERS CASES OF RENAL FAILURE AT OTC DOSES OF NSAIDS—Continued

	Ibuprofen	Naproxen Sodium	Ketoprofen
Renal Failure Cases—Pediatric	14	0	0

Next, Dr. Griffin discussed renal complications from the use of NSAIDs obtained from large population studies (Ref. 20). A study of patients 65 years of age and older in the Tennessee Medicaid database (Ref. 23) included the following information:

- Eighteen percent of the patients presenting with acute renal failure used NSAIDs at either prescription or OTC doses. A RR for acute renal failure in NSAID users was calculated to be 1.58 compared to NSAID non-users.
- The RR for acute renal failure with ibuprofen was dose related. The RR of acute renal failure associated with use of daily doses of less than 1,200 mg was approximately 1 compared to use of no ibuprofen. Daily doses of 1,200 to 2,400 mg (above the OTC range of 1,200 mg per day or less) increased the RR of renal failure to 1.89.
- The greatest risk for renal failure was within the first 30 days of therapy with an NSAID. The RR was 2.83.

Several drug manufacturers and others provided additional comments (Ref. 4). One drug manufacturer stated that the incidence of renal failure and other serious renal events are rare with use of either prescription or OTC ibuprofen. One drug manufacturer claimed that there was an average of approximately five reports of renal failure per year from FDA's safety surveillance data. The manufacturers also suggested that serious renal events are almost always reversible, even in the elderly or chronically ill. It was stated that serious renal events following NSAID therapy almost always occur in patients with pre-existing renal dysfunction, congestive heart failure, or compromised hepatic function.

Several drug manufacturers submitted additional information suggesting that (Ref. 5):

- The number of renal side effects that have been reported with OTC ibuprofen are minimal (less than two cases of renal failure per year), confirming that the drug is well-tolerated.

- The renal safety profile of naproxen/naproxen sodium is consistent with other currently marketed NSAIDs with which it has been compared. Even at prescription doses, reports of adverse events involving the kidney have been rare.

3. NDAC Deliberations and Recommendations Concerning Aspirin and Other NSAIDs

- *GI bleeding*. NDAC members agreed that NSAIDs increase the risk for GI adverse events. The risk appears to be related to dose. Aspirin, even at lower doses, has some GI risks. However, the benefits from use far exceed any risks. NDAC stated that low dose aspirin should be available OTC for the elderly for cardiovascular prophylaxis as described in the professional labeling. NDAC believed that the absolute risk of GI bleeding from use of low dose aspirin is probably comparable to the risk from using aspirin at analgesic doses. Therefore, NDAC recommended that the information on risk provided in OTC aspirin labeling to consumers need not be categorized by dose.

NDAC agreed that the data support a separate and distinct stomach bleeding warning and suggested that the heading ''stomach bleeding warning'' be used. NDAC recommended that this heading be in bold type and that the warning be included as one of the first warnings in labeling along with the Reye's syndrome warning. One NDAC member suggested the heading ''bleeding alert'' because aspirin and the other NSAIDs can cause more than

stomach bleeding, and it is very important to stop using an OTC IAAA active ingredient when signs of bleeding are present (e.g., vomiting blood or bloody or black stools). Most NDAC members felt that stomach bleeding was the major safety problem and should be the focus of the warning statement.

NDAC found that low dose aspirin, combined with another NSAID, will increase the risk for GI bleeding two to four times more than use of an NSAID alone. From the data reviewed, enteric-coated or buffered aspirin preparations do not change the risk associated with use of multiple NSAID products. NDAC recommended that the labeling for aspirin and other NSAIDs include a stomach bleeding warning advising consumers of the risks of taking more than directed or using more than one NSAID. In addition, NDAC concluded that the warning should advise consumers that the risk is greater for individuals who are over 65 years of age, have a history of ulcers, stomach, or bleeding problems, or are taking steroids or anticoagulants (blood thinners).

A majority of NDAC members believed that there were insufficient data and a lack of a scientific rationale to support a warning about using alcohol while taking NSAIDs. Recognizing that the data are mixed and not conclusive, the members believed that a majority of the trials reviewed failed to show a direct and convincing association with alcohol. NDAC urged FDA to remove the existing alcohol warning from labeling and encouraged FDA to examine future cases of GI bleeding in individuals who consume alcohol and are alcohol abusers to explore the impact of concomitant use of NSAIDs.

- *Renal effects*. NDAC considered particular groups at risk for short-term adverse renal consequences from NSAID use. While NDAC agreed that small increases in blood pressure of limited duration (e.g., several days) in normotensive or hypertensive individuals is not a significant risk, the labeling

for NSAIDs should warn about the potential association of long-term use and renal failure in individuals who have high blood pressure, heart or kidney disease, use diuretics, or are over 65 years of age. NDAC agreed with the OTC labeling proposed for ibuprofen in the **Federal Register** of August 21, 2002, including the warning to ask a doctor before use in the presence of high blood pressure, heart or kidney disease, if also using a diuretic, or if over 65 years of age.

Labeling. NDAC members agreed that labeling continues to be a major factor in promoting the safe and effective use of OTC NSAID products. NDAC expressed concern that consumers do not read labels adequately and are often unaware of the names of the medicines that they are taking. This lack of awareness is especially problematic for people who are also taking prescription medicines concomitantly with OTC drug products. NDAC expressed concern about the ability to communicate meaningful information in the confines of a small package label, especially to the elderly. NDAC suggested that patient information be included in a package insert to provide expanded information beyond what could be presented clearly on a small label.

NDAC strongly recommend that the term ''NSAID'' be used throughout OTC product labeling. The term NSAID is becoming more widely recognized and is often found in drug information leaflets. NDAC suggested that meaning of the NSAID acronym could be spelled out somewhere on the label. Additionally, NDAC recommended that this term should be included on the front panel or PDP, advising consumers that the product contains an NSAID, especially if the product is a combination containing an NSAID. Finally, NDAC members agreed that there is a need for additional label comprehension studies to identify ways to improve communication with consumers.

IV. FDA's Review of Additional Data and Information

A. Pre-existing Liver Disease as a Risk Factor for Acetaminophen Hepatotoxicity

Following publication of the OTC IAAA TFM in 1988, FDA received comments urging adoption of a warning to advise consumers with pre-existing liver disease against using acetaminophen, unless directed by a doctor. The comments cited reports in the medical literature concerning toxicity in persons with liver disease. Other comments asserted that there is no evidence to warrant a warning. At that time, FDA believed the evidence was insufficient to propose a warning. NDAC briefly discussed this issue in September 2002, but concluded that there were not sufficient data to make specific recommendations.

FDA has reconsidered its previous position on this issue and now believes that the current evidence supports a warning. At the NDAC meeting, FDA reported information derived from mortality data of acetaminophen overdose (intentional and unintentional). Among patients with chronic alcoholic or other chronic liver disease, death associated with unintentional acetaminophen overdose was reported far more frequently than in association with intentional overdose (see table 4 of this document). In the series of 282 AERS cases of hepatoxicity associated with acetaminophen use presented at the meeting, 70 cases were reported as having underlying liver disease.

Metabolic activation and deactivation are involved in acetaminophen elimination (Ref. 25). At a therapeutic dose, the majority (greater than 90 percent) of acetaminophen combines with glucuronic acid (the major metabolic pathway for adults) and sulfuric acid (the major metabolic pathway for children). There is also a second, minor metabolic pathway in which a small

portion of acetaminophen undergoes cytochrome P450 phase I metabolism to the toxic acetaminophen metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). This toxic metabolite is normally inactivated through combination with hepatic glutathione (GSH). Any factors that can change GSH availability (by decreasing synthesis and/or increasing utilization or interfering with the conjugation enzyme) could potentially influence the hepatotoxicity of acetaminophen. Any factors that disturb the balance between these two metabolic pathways may affect the amount of acetaminophen metabolized by each pathway. After the NDAC meeting, FDA conducted a literature review (1966 to January 2003) and determined that the following factors may place patients with pre-existing liver disease at a greater risk for acetaminophen toxicity (Ref. 26).

- Depletion of hepatic GSH has been found in both alcoholic and nonalcoholic liver diseases, suggesting that the diseased liver may have less capacity to inactivate the toxic metabolite of acetaminophen. (Refs. 27 through 34)

- The hepatic cytochrome P450 enzyme, P450–2E1, metabolizes acetaminophen to the toxic metabolite that causes hepatotoxicity. Expression of hepatic P450–2E1 tends to increase in stable chronic liver diseases.

- Studies have shown that the clearance of acetaminophen from the body is impaired in people with chronic liver disease (Refs. 35, 36, and 37). The disease status of the liver alters drug metabolism and drug metabolites made by each metabolic pathway (Refs. 38 and 39).

- In chronic liver disease, hepatic glucuronide and sulfate conjugation are decreased (Refs. 40 through 43).

- Significant impairment of total hepatic P450 expression is found only in people with severe liver disease (hepatitis with liver failure and decompensated cirrhosis) (Ref. 38). Recent studies indicate that different types (viral, chemical, or immunological factors) and/or states (acute, chronic, or severe) of liver disease selectively influence expression of different P450 isozymes.

- Chronic alcohol use significantly induces hepatic P450–2E1 and increases this enzyme's ability to metabolize acetaminophen to NAPQI (Ref. 44). In other types of human liver disease, changes in expression and activity of P450–2E1, as well as other P450 isozymes (1A2 and 3A4) involved in acetaminophen metabolism, are variable (Refs. 38, 45, 46, and 47). Both human and animal studies show that hepatic P450–2E1 expression is significantly increased in a nonalcoholic fatty liver (Refs. 48 and 49).

Few clinical trials directly assess the hepatotoxicity of acetaminophen in people with nonalcoholic liver disease. One double-blind, placebo controlled, crossover study was conducted in 20 people with stable chronic liver disease (including Laennec's cirrhosis, alcoholic liver cirrhosis, primary biliary cirrhosis, or chronic hepatitis) (Ref. 50). The subjects received 1 g of acetaminophen or placebo every 4 hours (a total of 4 g/day) for 13 days. The author stated that there were no significant changes in laboratory tests or clinical status in the acetaminophen and placebo treatments. The author concluded that underlying liver disease does not increase patient sensitivity to the hepatotoxic effects of acetaminophen at a therapeutic dose. Because of the small sample size and crossover study design, FDA believes this study is inadequate to make any conclusions regarding the risk for acetaminophen hepatotoxicity in patients with chronic liver disease.

In summary, the single prospective clinical study found by FDA in the literature that evaluated the susceptibility of the diseased liver to acetaminophen toxicity was not definitive. Analyses of an acetaminophen overdose database and a review of the AERS case reports suggest, however, that people with a history of liver disease may have increased susceptibility to acetaminophen-induced hepatotoxicity. In addition, the depletion of hepatic GSH has been found in both alcoholic and nonalcoholic liver diseases, suggesting that the diseased liver may have less capacity to inactivate the toxic metabolite of acetaminophen. Expression of hepatic P450–2E1, a major enzyme for metabolic activation of acetaminophen, tends to be increased in stable chronic liver diseases, particularly in nonalcoholic fatty liver disease. FDA believes that these data collectively establish that it is necessary to alert patients with chronic liver disease that they may be at risk for developing acetaminophen hepatotoxicity, as an important factor in the safe and effective use of acetaminophen products.

B. Updated Literature About Acetaminophen Hepatoxicity

The Acute Liver Study Group recently published an update of the prospective data in patients diagnosed with ALF at 22 tertiary care centers. Over a 6-year period from January 1, 1998, to December 31, 2003, 662 patients fulfilled standard criteria for ALF. Of these cases, 275 were attributed to acetaminophen hepatotoxicity. The criteria for attribution to acetaminophen included one or more of the following: (1) A history of potentially toxic acetaminophen ingestion (> 4 g/day) within 7 days of presentation; (2) detection of any level of acetaminophen in the serum; or (3) a serum alanine aminotransferase (ALT) > 1,000 IU/L with a history of acetaminophen ingestion, irrespective of acetaminophen level (Ref. 51).

Of the 275 cases attributed to acetaminophen, the following observations were made:

- 48% were designated as unintentional injury, 44% were designated as an intentional injury and 8% could not be classified to either group;
- 147 (53%) used an OTC product, including 6 of 147 who used more than one OTC product at the same time and 41 of 147 who also used a prescription combination product;
- 120 (44%) reported use of a narcotic/acetaminophen combination;
- 55% had a history of alcohol use and 35% had a history of alcohol abuse;
- 108 (39%) also used a antidepressant;
- 65% survived without transplant; and
- 22% used more than one acetaminophen product.

The authors also compared characteristics between those classified as unintentional versus intentional liver injury. Females predominate in both groups. The clinical outcomes are similar for both groups. Narcotic/ acetaminophen use was more prevalent in the unintentional injury group (63% vs. 18%). The unintentional injury group had a greater percentage with stage 3-4 hepatic coma score at admission and at peak during the hospitalization. FDA believes that these data support the previous NDAC conclusion that acetaminophen hepatotoxicity is an important public health consideration and that additional labeling is necessary for it to continue to be generally recognized as safe and effective.

C. Aspirin and Other NSAIDs

1. GI Bleeding

Following the NDAC meeting, FDA reviewed additional data and information related to the use of OTC NSAIDs and GI bleeding.

- One individual asserted in a citizen petition that incomplete information about aspirin reaches consumers and increases the danger that aspirin will be misused with serious consequences (Ref. 52). The citizen petition suggested that additional labeling for aspirin should be implemented without delay to state: ''CAUTION: This product can cause severe hemorrhaging and should not be taken for more than five days except under the supervision of a physician. When used for fever, if symptoms persist more than three days, consult a physician.''

- NSAIDs are being used by an estimated 17 million Americans on a daily basis (Ref. 53). The estimated rate of serious adverse events is about 1 percent for clinically significant GI bleeding in the first 3 months of use (Ref. 54). NSAID use is so widespread that NSAID-induced gastropathy has been identified by some as one of the most prevalent, serious drug toxicities in the United States (Ref. 55). NSAID-associated serious GI complications are estimated to result in over 200,000 hospitalizations per year in the United States. Although these adverse event rates are for prescription and OTC NSAID formulations combined, there is a significant prevalence of OTC NSAID use among people presenting to hospitals with upper GI bleeding (Ref. 56). The rate of consumption of OTC NSAIDs by consumers is estimated to be as much as seven times that of prescribed NSAIDs (Ref. 54).

- The American College of Gastroenterology guideline for treatment and prevention of NSAID-induced ulcers indicates an increased risk of NSAID-

associated GI complications for people greater than 60 years of age (Ref. 56). A United Kingdom (UK) population-based, retrospective case-control study evaluated the risk of various NSAIDs (Ref. 10). The study reported a RR of 3.7 for upper GI bleeding (UGIB) and GI perforation in people under 60 years old exposed to NSAIDs, 13.2 in people 60 years and older exposed to NSAIDs, and 2.8 in people 60 years and older not exposed to NSAIDs.

- FDA analyzed a series of studies that used the Medicaid population in Tennessee (Refs. 12, 13, 56, 57, and 58). These case-controlled retrospective studies were based on hospitalizations for GI bleeds. The study population totaled 103,954 individuals, about 15 percent of Tennessee's elderly population, with 209,066 person-years of followup. There were 1,371 hospitalizations for PUD. These studies found increased risk of GI bleeds in people who were:
  - Over 65 years old (RR of 4.7),
  - Taking an increased NSAID dose (RR of 2.8 for the lowest dose vs. RR of 8 for the highest dose category), or
  - Taking concomitant corticosteroid (RR of 4.4) or anti-coagulant (RR 12.7) drug products.

In addition, the risk of GI bleeds among people taking NSAIDs was greatest within the first 30 days of use (RR of 7.2).

- A multicenter, case-control study of 550 people with UGIB admitted to a hospital with bloody stools or vomiting blood and 1,202 controls identified from census lists, compared risks of major GI bleeding for plain, coated, and buffered formulations of low-dose aspirin (Ref. 59). Each of these types of low-dose aspirin formulations (less than 325 mg per day) had about a 2.5 to 3 times increased risk of major UGIB.

- A double-blind, randomized, placebo-controlled, ulcer prevention study in 8,843 people with rheumatoid arthritis identified several risk factors for upper GI complications from NSAID use: (1) Age 75 years or older (odds ratio 2.48), (2) prior peptic ulcer (odds ratio 2.29), (3) prior GI bleeding (odds ratio 2.56), and (4) history of cardiovascular disease (odds ratio 1.84) (Ref. 60).
- A case control study of 1,122 subjects admitted consecutively for UGIB to four hospitals in Spain and 2,231 controls from the same geographic area, showed that a prior history of UGIB is a risk factor (odds ratio 3.7) for UGIB in people who used NSAIDs (Ref. 61).

In summary, results of several large-scale clinical studies, conducted in the United States and worldwide, have established that use of OTC NSAIDs is an important risk factor for serious GI adverse events, especially bleeding. The risk is higher for people age 60 or older, who have a history of stomach ulcers or bleeding problems, or who use corticosteroids or anticoagulants.

2. Renal Effects

NSAIDs decrease renal prostaglandin production, which may result in acute reduction in renal blood flow and glomerular filtration, leading to fluid retention, edema, and elevation of serum creatinine (Ref. 62). Marked reduction in renal blood flow may result in renal failure.

NSAID use may also result in higher than normal levels of potassium in the bloodstream. This occurs most commonly in people with diabetes mellitus or mild to moderate renal insufficiency as well as in people taking beta-blocker, angiotensin-converting enzyme inhibitor, or potassium-sparing diuretic drugs.

By inhibiting the production of vasodilatory prostaglandins, NSAIDs may decrease renal blood flow and the rate of glomerular filtration in subjects with

congestive heart failure, liver failure with ascites, chronic renal disease, or those who are hypovolemic (abnormal volume decrease of circulating fluid (plasma) in the body) (Refs. 63, 64, and 65).

a. Pediatric population. The medical literature includes sporadic reports of acute renal failure in pediatric subjects taking ibuprofen within the OTC dose range, including the following cases:

- One article describes three cases in children 5-, 6.5-, and 7.5-years-old in which ibuprofen treatment led to varying degrees of renal failure (Ref. 66). Two subjects with dehydration and pre-existing renal problems were prescribed ibuprofen for the treatment of fever due to acute illness. Both had a recovery of renal function on withdrawal of the drug. The third child (a 7.5-year-old girl) developed progressive chronic renal failure. She had underlying hyper Ig-E syndrome and was treated with a single dose of ibuprofen 5 mg /kg for fever due to severe pulmonary infection. Her illness was also complicated by moderate dehydration. Her renal biopsy showed evidence of kidney damage consistent with loss of blood circulation.

- Ibuprofen-induced acute renal failure was reported in a 9-month-old girl (Ref. 67). A family practitioner treated the infant for diarrhea, vomiting, and fever. She was given oral rehydration therapy and acetaminophen and was sent home. Symptoms persisted for 48 hours and the acetaminophen was changed to ibuprofen 50 mg (5 mg/kg/dose) three times a day. Seven doses of ibuprofen were given over a 40-hour period, but the child's clinical state deteriorated. She was admitted to an emergency facility 18 hours after the last dose with a creatinine concentration of 2.1 mg/deciliter (dL). For the first 12 hours after admission, the infant's kidneys failed to secrete urine in spite of receiving adequate hydration and an intravenous diuretic (furosemide). The creatinine

concentration increased to 2.4 mg/dL. Renal function slowly recovered; 4 days after admission her creatinine was 0.9 mg/dL and 3 weeks later was 0.5 mg/dL. Clinical diagnosis was kidney damage secondary to ibuprofen use in a dehydrated child.

- Primack, et al. reported acute renal failure with use of ibuprofen in an 11-year-old boy (Ref. 68). The child was diagnosed with possible sinusitis and given an antibiotic; on the third day symptoms worsened with associated headaches, fatigue and anorexia, and his serum creatinine was 0.7 mg/dL. The antibiotic was continued and ibuprofen 200 mg was added, alternating with acetaminophen every 4 hours for fever. He received a total of 24 200-mg ibuprofen tablets during the 12 days prior to hospitalization. The fever persisted with improvement in the other symptoms. The child became progressively weaker and began vomiting. Approximately 2 weeks after his illness began, the child was admitted with a serum creatinine of 7.6 milliequivalent/L. After 3 days of symptomatic treatment, his serum creatinine was 4.1 mg/dL and 1 week later his serum creatinine was 2.2 mg/dL. Findings of renal biopsy on the third hospital day were consistent with acute interstitial nephritis, which the authors attributed to beta-lactam antibiotic use.

These case reports demonstrate the variety of situations in which ibuprofen-associated renal toxicity can occur. In many of the cases, the children were already at risk for renal adverse effects because of underlying disease states, concomitant medications, or dehydration. Children with underlying illnesses or those dehydrated are at greatest risk for this injury. FDA currently requires all OTC pediatric products containing ibuprofen marketed under new drug applications to include warnings for children ages 2 to 11

years to ask a doctor before use if the child has ‘‘not been drinking fluids’’ or has ‘‘lost a lot of fluid due to continued vomiting or diarrhea.’’

b. Alcohol use. Binge drinking of alcohol reduces the production of antidiuretic hormone causing increased urine production. Two cases of reversible acute deterioration in renal function following binge drinking of beer with use of NSAIDs have been reported in adults (Ref. 69):

- The authors reported a case of a 22-year old male admitted to the hospital with low back pain and worsening renal function. Four days prior to admission, he had consumed an unknown amount of beer; 2 days later as the pain intensified he had taken six doses of 400-mg ibuprofen with no relief. Upon admission, his serum creatinine was 3.1 mg/dL. Biopsy of the kidney was consistent with the diagnosis of acute kidney failure. The subject’s serum creatinine increased to a peak of 6.5 mg/dL on the fourth day and decreased to 1.4 mg/dL 6 days later.

- In a second case, a 20-year old male was admitted because of flank and back pain of 24 hours’ duration. Four days before admission, the subject drank 8 to 10 bottles of beer (355 mL per bottle). On the evening of admission, he had taken 6 to 8 tablets of 325-mg aspirin for pain relief. The laboratory data showed a 2.0 mg/dL serum creatinine level. Following intravenous fluid administration, the subject urinated frequently for over 16 hours. Followup serum creatinine 1 week later was 1.2 mg/dL. The authors concluded that dehydration is a frequent consequence of heavy alcohol ingestion due to water diuresis. The volume contraction may be further aggravated by nausea and vomiting.

In the proposed rule to amend the TFM for OTC IAAA drug products to include ibuprofen, FDA included the results of the agency’s evaluation of the

adverse renal effects of OTC doses of ibuprofen (67 FR 54139 at 54144). Based on its evaluation of the data, FDA concluded that OTC doses of ibuprofen can exert a variety of adverse renal effects, particularly in those who are dependent on adequate prostaglandin levels to maintain renal hemodynamic perfusion (i.e., congestive heart failure, liver failure with ascites, etc.). It was further noted that although the sporadic nature of idiosyncratic drug-induced ibuprofen nephrotoxicity makes it impossible to predict which group of individuals is at risk for developing this event, this is not the case with individuals who experience prostaglandin-dependent hemodynamic changes. The latter, if recognized, is reversible upon discontinuation of the drug (67 FR 54139 at 54145).

V. FDA's Tentative Conclusions

FDA has carefully considered NDAC's recommendations and other available data and information and determined that labeling revisions are necessary for OTC IAAA drug products to advise consumers of potential health risks and to recommend, under certain circumstances, that they consult a doctor for advice about taking products containing OTC IAAA active ingredients.

FDA continues to believe that acetaminophen and NSAIDs, when labeled appropriately and used as directed, are generally recognized as safe and effective OTC IAAA drugs for consumer self-use. However, the available evidence clearly indicates that both drugs can cause serious side effects. When taken in excess amounts, acetaminophen can cause liver injury. NSAIDs have the potential to cause GI bleeding and renal (kidney) injury even at OTC dosing levels.

When compared to the extensive use of OTC acetaminophen and NSAID drug products, the incidence of injury appears relatively low. However, based on the available evidence and the seriousness of the risks, FDA believes it is necessary for consumers to be made aware of the possible serious side effects associated with using these products. For many people, the risks are quite low because they use these products only occasionally. The risks may be greater for people who use these products more frequently, have certain risk factors, and/or do not follow the labeling information on the package. FDA believes that providing additional labeling information about how to correctly use OTC drug products containing acetaminophen and NSAIDs could reduce injuries and is necessary for the products to be considered generally recognized as safe and effective and not misbranded.

FDA plans to act on several fronts:

- Propose revised OTC labeling for these products
- Continue a consumer and health provider educational campaign
- Continue to monitor AERS in various databases
- Examine available data to determine whether other measures may be needed in the future to try to decrease morbidity associated with OTC acetaminophen and NSAIDs.

In addition to the changes to the IAAA TFM proposed in this document, FDA encourages manufacturers of these products to undertake education initiatives regarding safe use of OTC products containing acetaminophen and NSAIDs. FDA plans to increase its monitoring of AERS in various databases to see how this new proposed labeling, if implemented, is working to reduce injuries resulting from OTC acetaminophen and NSAID drug products and to determine whether further measures need to be proposed.

A. Acetaminophen

1. Hepatotoxicity

FDA tentatively concludes that additional new labeling is needed for OTC drug products that contain acetaminophen. Data from Lee (Ref. 6), a case series from the University of Pennsylvania Hospital (Ref. 4), and the FDA AERS database show that unintentional overuse of acetaminophen is associated with severe hepatic injury. One manufacturer provided calculations of a ''worst case'' scenario for acetaminophen hepatic failure deaths using estimates by Lee (Ref. 70) and calculated 213 deaths per year. FDA does not know the exact number of cases of liver failure or deaths related to unintentional acetaminophen overdose. FDA thinks that improved labeling may help prevent events that are catastrophic to the unintentional victims and their family members. FDA has determined that adding a liver warning is necessary for safe and effective use of the drug and to reduce the number of unintentional overdoses. Thus, FDA is proposing a ''liver warning'' stating use factors that could lead to liver injury.

FDA notes that NDAC recommended both an alcohol warning and a liver toxicity statement separate from the alcohol warning for OTC drug products containing acetaminophen. FDA has combined this information because it is interrelated and a shorter warning saves label space on products that already contain extensive labeling information. FDA believes that two, separate warnings may be less likely to be read and understood by consumers.

FDA also tentatively concludes that a new warning is needed to advise consumers who have liver disease to consult a doctor before using OTC drug products that contain acetaminophen. FDA notes that many of the case reports in the databases involved people who had pre-existing liver disease (the rate

of the number of cases in the databases exceeds the rate of underlying liver disease in the general population). This observation may also be due to a difference in the use of acetaminophen by people with chronic liver disease or that they are at greater risk to develop liver failure in general. As described in section IV.A of this document, people with chronic liver disease can have changes in the liver enzymes responsible for the metabolism of acetaminophen. It is not clear whether these changes increase the risk in these individuals. It was noted at NDAC that some physicians who treat patients with chronic liver disease recommend lower total daily doses. FDA believes this additional warning will alert patients with chronic liver disease to ask their doctor before using acetaminophen. FDA recognizes there is limited information supporting the need for different dose recommendations in people with liver disease. FDA seeks comment on the information this warning should provide and encourages healthcare providers and researchers who treat patients with chronic liver disease to provide information on how much they recommend as an appropriate dose and the basis for their recommendation.

2. Other Labeling

FDA also tentatively concludes that the name ''acetaminophen'' on the PDP should be enhanced to allow consumers to better identify acetaminophen containing products among the many products currently available on the OTC market. First, FDA is proposing that the name be highlighted (e.g., in fluorescent or color contrast to other information on the PDP) or in bold type so that the name is prominent and stands out from other text. Second, FDA is proposing that the name have a size that is prominent compared to other printed matter on the PDP. FDA's regulation for the statement of identity for OTC drug products in § 201.61(c) (21 CFR 201.61(c)) states that ''the statement

of identity shall be presented in bold face type on the PDP, shall be in a size reasonably related to the most prominent printed matter on such panel ***.'' FDA is proposing that manufacturers determine the prominence of the name ''acetaminophen'' on the PDP by selecting, from the two options that follow, the print size option that is greater:

- The name ''acetaminophen'' is at least one-quarter as large as the size of the most prominent printed matter on the PDP; or
- The name ''acetaminophen'' is at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2) (21 CFR 201.66(d)(2)).

Finally, FDA notes that NDAC expressed concern about the lack of standardized pediatric dosage information, especially for infants under 2 years of age. FDA intends to address this issue in another **Federal Register** publication.

B. Aspirin and Other NSAIDs

1. GI Bleeding

FDA tentatively concludes that epidemiological data indicate a dose-related risk for GI bleeding with NSAIDs. The data demonstrate a slight increase in risk for GI bleeding at OTC daily doses. Because many people use OTC NSAIDs intermittently, the risk for bleeding for the average person is quite low. People who use NSAIDs for several days may be at greater risk but it is still low compared to chronic NSAID users. People who have certain identifiable risk factors (e.g., stomach ulcers or bleeding problems, taking certain other drugs or alcohol concurrently) are at greater risk of GI bleeding when they take a product containing an NSAID. FDA believes that additional warnings alerting these people about these potential risks and some of the

symptoms associated with GI bleeding could reduce morbidity from using these OTC NSAID drug products.

Based on the NDAC's recommendations and the agency's review of the literature, FDA has determined that additional new warning labeling is needed to continue to consider OTC NSAID products generally recognized as safe and effective. Such warnings should advise people not to take more than one product containing NSAIDs (aspirin, ibuprofen, naproxen, or others) and not to take more drug or take the drug for a longer time than recommended in product labeling. NDAC also acknowledged that people age 65 and older are at increased risk for GI bleed.

FDA subsequently reviewed the results of several large-scale clinical studies, conducted in the United States and worldwide, and has established that use of NSAIDs is an important risk factor for serious GI adverse events, especially bleeding. These studies show that the risk is higher for people age 60 or older, who have had stomach ulcers or bleeding problems, or who use corticosteroids or anticoagulants (Refs. 10 and 55). Based on these studies, FDA believes that people 60 years of age and older are at increased risk and is proposing to include this age group in the warning.

In September 1993, NDAC concluded that the use of aspirin, ibuprofen, and naproxen sodium increases the risk of UGIB in people who are heavy alcohol users or abusers. At the September 2002 meeting, during discussion of the relative risks for GI bleeding associated with the use of OTC NSAIDs, some NDAC members questioned whether the incidence of GI bleeding is increased by the concurrent use of NSAIDs and alcohol. NDAC members were divided almost equally. Some members thought that there was no clear evidence that alcohol potentiates the risk of bleeding in NSAID or aspirin

users. They proposed removal of the existing alcohol warning. Other NDAC members suggested that the alcohol warning should remain in effect, but be separated from the GI bleeding warning.

Subsequently, FDA considered NDAC's recommendations and evaluated the alcohol warning for OTC drug products containing an NSAID. FDA did a new literature search, selecting new articles describing the relationship between alcohol use and the risk of GI bleeding in OTC IAAA users. After reviewing these articles (Ref. 71), FDA finds that these studies, despite some flaws in their design and methodology, suggest that combining NSAIDs with alcohol increases the risks of a GI bleed. FDA has determined that it is necessary to retain a warning regarding use of OTC NSAID drug products with alcohol. FDA tentatively concludes that a warning about this risk should be incorporated in a ''Stomach bleeding warning'', in place of the current alcohol warning. Although NDAC recommended that a GI bleeding warning be distinct from a warning against alcohol ingestion with NSAIDs, FDA is proposing to combine these two warnings to conserve labeling space and avoid redundancy.

2. Renal Effects

FDA tentatively concludes that people who get acute renal insufficiency from using NSAIDs generally have a pre-existing condition that will predispose them to this insufficiency. There is a pharmacological basis for this to occur. Normal renal blood flow depends on prostaglandin metabolism. NSAIDs inhibit renal prostaglandin production. In predisposed people, suppression of prostaglandin production may result in acute reduction in renal blood flow and glomerular filtration, leading to renal insufficiency. These cases are often reversible. Although the epidemiological data are limited and the number of reported cases are rare relative to their use, FDA believes it is important to

alert consumers about underlying conditions that may increase their risk if they take an NSAID without first asking a doctor because of potential serious side effects.

NDAC agreed with the OTC labeling proposed for ibuprofen in the **Federal Register** of August 21, 2002, including the warning to ask a doctor before use in the presence of high blood pressure, heart or kidney disease, concomitant use of a diuretic, or if they are over 65 years of age. Based upon a further review of the literature that indicates that the risk is higher for people age 60 or older, FDA is proposing to lower the age from 65 years of age to 60 years of age.

Children's NSAID products marketed under an NDA already have warnings regarding dehydration and fluid loss. FDA tentatively concludes that similar language is needed for children's NSAIDs products marketed under the OTC drug monograph. There are, however, few case reports suggesting a problem in adults. FDA is seeking comment on the need for similar language for adults. Although there are few reported cases in adults, it is anticipated that prostaglandin has similar effects on renal physiology.

3. Other Labeling

FDA agrees with NDAC that the term ''NSAID'' should be prominently displayed in OTC drug product labeling so consumers are aware of the presence of the ingredient in the product. The term should also be defined in the labeling as ''nonsteroidal anti-inflammatory drug.'' FDA tentatively concludes that the presence of an ''NSAID'' ingredient in an OTC drug product should be prominently stated on the PDP and in the Drug Facts labeling.

In section V.A.2 of this document, FDA discusses its proposed requirements for the name ''acetaminophen'' to be prominently presented on

the PDP. FDA considers the same degree of prominence necessary to identify the presence of an ''NSAID'' ingredient in an OTC IAAA drug product. Accordingly, FDA is proposing that the name of the NSAID ingredient and the word ''(NSAID)'' be highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2). In the Drug Facts labeling, FDA is proposing that the active ingredient(s) section, as defined in § 201.66(c)(2), be required to contain the term ''(NSAID)'' after the NSAID active ingredient with an asterisk statement at the end of the active ingredient(s) section that defines the term ''NSAID'' as a '' * nonsteroidal anti-inflammatory drug.''

In addition, FDA has conducted a detailed review of available data regarding the potential risks of serious cardiovascular events in patients receiving COX–2 selective and non-selective NSAIDs. FDA also held a joint meeting of its Arthritis and Drug Safety and Risk Management on February 16–18, 2005, to consider these issues. FDA is currently considering whether additional labeling changes related to these risks are warranted, and will address this in a future issue of the **Federal Register**.

VI. FDA's Proposal

Based on the available evidence, FDA is proposing to amend its regulations and the OTC IAAA TFM to make a number of changes. FDA is proposing new labeling for OTC IAAA drug products (proposed § 201.325). This labeling includes a number of important new warnings. To alert

consumers to these new warnings, FDA is proposing to require that the statement ''See new warnings information'' appear on the PDP of all OTC IAAA drug products for a limited time after the effective date of a final rule based on this proposal (proposed § 201.325(b)).

The labeling statements in this proposed rule are in the OTC Drug Facts labeling format (see § 201.66), which is being implemented for all OTC drug products. For ease of reading, the following descriptions of the proposed labeling statements do not include the bracketed formatting instructions included in the codified portion of this document.

A. Alcohol Warning

FDA is proposing to remove § 201.322 of the regulations entitled ''Over-the-counter drug products containing internal analgesic/antipyretic active ingredients required alcohol warning.''

B. Acetaminophen

1. For All Acetaminophen Products

Proposed § 201.325(a)(1)(i) includes the following provisions:

- The presence of acetaminophen in the product must be prominently stated on the PDP. The word ''acetaminophen'' must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2).

- The presence of acetaminophen must appear as part of the established name of the drug, as defined in § 299.4 (21 CFR 299.4).

- Combination products containing acetaminophen and a non-analgesic ingredient(s) (e.g., cough-cold) must include the name ''acetaminophen'' and the names of the other active ingredients in the product on the PDP. Only the name ''acetaminophen'' must appear highlighted (e.g., fluorescent or color contrast) or in bold type, and be in one of the following sizes, whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2).

2. For Acetaminophen Products Labeled for Adults Only

Under proposed § 201.325(a)(1)(iii), the labeling would be required to include the following statement:

Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take

- more than (insert maximum number of daily dosage units) in 24 hours
- with other drugs containing acetaminophen
- 3 or more alcoholic drinks every day while using this product.

This ''Liver warning'' would be the first warning under the ''Warnings'' heading. For products that contain both acetaminophen and aspirin, the ''Liver warning'' would appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B) and before the NSAID ''Stomach bleeding warning'' in proposed § 201.325(a)(2)(iii)(A).

The labeling would also be required to include the statements ''Do not use with any other drug containing acetaminophen (prescription or

nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure'' and ''Ask a doctor before use if you have liver disease.''

3. For Acetaminophen Products Labeled Only for Children Under 12 Years of Age

Under proposed § 201.325(a)(1)(iv), the labeling would be required to include the following statement:

Liver warning: This product contains acetaminophen. Severe liver damage may occur if the child takes

- more than 5 doses in 24 hours
- with other drugs containing acetaminophen.

This ''Liver warning'' must be the first warning under the ''Warnings'' heading.

The labeling would also be required to include the statements ''Do not use with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure'' and ''Ask a doctor before use if the child has liver disease.''

FDA is aware that products labeled for children only are sometimes used by adults who cannot take solid oral dosage forms or who are taking a product marketed in children's strengths. Accordingly, FDA is proposing to include the statement ''this product does not contain directions or warnings for adult use'' in bold type in the labeling of these products under the heading ''Directions''.

4. For Acetaminophen Products Labeled for Adults and Children Under 12 Years of Age

Under proposed § 201.325(a)(1)(v), the labeling would be required to include all of the warnings for adults with the following modifications:

Liver warning: This product contains acetaminophen. Severe liver damage may occur if

- adult takes more than [insert maximum number of daily dosage units] in 24 hours
- child takes more than 5 doses in 24 hours
- taken with other drugs containing acetaminophen.
- adult has 3 or more alcoholic drinks every day while using this product.

This ''Liver warning'' must be the first warning under the ''Warnings'' heading. FDA is proposing to use the term ''the user'' instead of ''you or the child'' for warnings applying to both children and adults. The ''ask a doctor'' statement is modified to read: ''Ask a doctor before use if the user has liver disease.''

C. Aspirin and Other NSAIDs

The NSAID category includes, but is not limited to, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate. In the **Federal Register** of August 21, 2002 (67 FR 54139 at 54159), FDA proposed a number of warnings for products containing ibuprofen if added to the OTC IAAA drug products monograph. FDA is adding information and further revising portions of some of those warnings in this document and proposing these warnings be applicable to all OTC NSAIDs.

1. For All Products Containing NSAIDs

Proposed § 201.325(a)(2)(i) includes the following provisions:

- The presence of an NSAID ingredient in the product must be prominently stated on the PDP. The name of the NSAID ingredient and the word ''(NSAID)'' must appear highlighted (e.g., fluorescent or color contrast)

or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2).

- For single ingredient products, the word ''(NSAID)'' must appear as part of the established name of the drug, as defined in § 299.4 of this chapter, or as part of the statement of identity of the drug, as defined in § 201.61 of this chapter. For example, either of the following would be acceptable:

- Ibuprofen Tablets (NSAID)

Pain reliever/ fever reducer

or

- Ibuprofen Tablets

Pain reliever/ fever reducer (NSAID)

- Combination products containing an NSAID and a non-analgesic ingredient(s) (e.g., cough-cold) must include the name of the NSAID ingredient and the names of the other active ingredients in the product on the PDP. The word ''(NSAID)'' must appear after either the name of the NSAID ingredient or the general pharmacological (principal intended) action of the NSAID ingredient (see previous examples). Only the name of the NSAID ingredient and the word ''(NSAID)'' must appear highlighted (e.g., fluorescent or color contrast) or in bold type, and be in one of the following sizes, whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2).

2. For NSAID Products Labeled for Adults Only

Warnings for NSAIDS are proposed in § 201.325(a)(2)(iii). Some of the proposed warning statements are discussed here.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed.

This ''Stomach bleeding warning'' would appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). For products that contain both acetaminophen and aspirin, the acetaminophen ''Liver warning'' would appear before the NSAID ''Stomach bleeding warning.''

The labeling would be required to include the following statement:

Ask a doctor before use if you have

- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- taken a diuretic

- reached age 60 or older.

The labeling would be required to include the statement:

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug

The labeling would be required to include the statement:

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- stomach pain or upset gets worse or lasts

3. For NSAID Products Labeled Only for Children Under 12 Years of Age

Under proposed § 201.325(a)(2)(iv), the labeling would be required to include the following statement:

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if the child:

- has had stomach ulcers or bleeding problems
- takes a blood thinning (anticoagulant) or steroid drug
- takes other drugs containing an NSAID (aspirin, ibuprofen, naproxen, or others)
- takes more or for a longer time than directed.

The ''Stomach bleeding warning'' would appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B).

The labeling would be required to include the following statement:

Ask a doctor before use if the child has

- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- not been drinking fluids
- lost a lot of fluid due to vomiting or diarrhea
- high blood pressure
- heart or kidney disease
- taken a diuretic.

The labeling would be required to include the statement:

Ask a doctor or pharmacist before use if the child is

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug

The labeling would also be required to include the statement:

Stop use and ask a doctor if

- the child feels faint, vomits blood, or has bloody or black stools. These are signs of stomach bleeding.
- stomach pain or upset gets worse or lasts

FDA is aware that products labeled only for children are sometimes used by adults who cannot take solid oral dosage forms or who are taking a product marketed in children's strengths. Accordingly, FDA is proposing to include the statement ''this product does not contain directions or warnings for adult use'' in bold type in the labeling of these products under the heading ''Directions''.

4. For NSAID Products Labeled for Adults and Children Under 12 Years of Age

Under proposed § 201.325(a)(2)(v), the labeling would be required to include all of the warnings for adults with the following modifications:

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if the user:

- has had stomach ulcers or bleeding problems
- takes a blood thinning (anticoagulant) or steroid drug
- takes other drugs containing an NSAID (aspirin, ibuprofen, naproxen, or others)
- takes more or for a longer time than directed
- is age 60 or older
- has 3 or more alcoholic drinks everyday while using this product.

The ''Stomach bleeding warning'' would appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B).

FDA is proposing to use the term ''the user'' instead of ''you or the child'' for warnings applying to both children and adults in the above and following modified statements.

The labeling would be required to include the following statement:

Ask a doctor before use if the user has

- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure

- heart or kidney disease
- taken a diuretic
- not been drinking fluids
- lost a lot of fluid due to vomiting or diarrhea
- reached age 60 or older

The labeling would be required to include the statement:

Ask a doctor or pharmacist before use if the user is

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug

The labeling would also be required to include the statement:

Stop use and ask a doctor if

- the user feels faint, vomits blood, or has bloody or black stools. These are signs of stomach bleeding.
- stomach pain or upset gets worse or lasts.

5. Active Ingredients

Under proposed § 201.325(a)(2)(v), the active ingredient(s) section of the product's labeling, as defined in § 201.66(c)(2), would be required to contain the term ''(NSAID)*'' after the NSAID active ingredient with an asterisk statement at the end of the active ingredient(s) section that defines the term ''NSAID'' as a ''* nonsteroidal anti-inflammatory drug.''

D. Requirements to Supplement Approved Applications

Holders of approved applications for OTC IAAA drug products who voluntarily implement the proposed labeling changes in proposed § 201.325(a) would be required to submit supplements under § 314.70(c) (21 CFR 314.70(c)), but could implement the proposed labeling without advance approval from

FDA, provided the labeling includes the information in proposed § 201.325(a). See section IX of this document on voluntary implementation.

E. Regulatory Action

Proposed § 201.325(c) sets out the implementation dates for the proposed labeling changes after publication of any final rule based on this proposal. See section VIII.B of this document on marketing conditions.

F. Conforming Changes to the OTC IAAA TFM

This proposed rule includes changes to the OTC IAAA TFM in proposed § 343.50. Proposed § 343.50(c)(1)(i), (c)(1)(iii), (c)(1)(iv)(A), (c)(1)(v)(A), (c)(1)(v)(B), (c)(1)(v)(C), (c)(1)(ix)(A), (c)(1)(ix)(B), (c)(1)(ix)(C), (c)(1)(ix)(E), (c)(2)(i), (c)(2)(iii), (c)(2)(iv)(A), (c)(2)(v)(A), (c)(2)(v)(B) and (c)(2)(v)(C) (as proposed in 53 FR 46204 and 67 FR 54139) would be amended and new paragraphs (b)(4)(i)(c) and (c)(3)(i) through (c)(3)(v)(C) would be added to either include references to proposed § 201.325 and/or additional language to conform to that section.

VII. Additional Issues for Consideration

A. Safe and Effective Daily Acetaminophen Dose

In 1960, FDA first approved (under the NDA process) a 325-mg immediate-release acetaminophen tablet formulation for OTC marketing in the United States. The recommended dose was one to two tablets every 4 to 6 hours, with a maximum daily dose of 3,900 mg in a 24-hour period (Ref. 3).

In 1973, FDA approved (under the NDA process) a 500-mg immediate-release acetaminophen capsule formulation for OTC marketing in the United States. The sponsor's rationale for this product was that the higher strength would have greater analgesic efficacy. Four double-blind, placebo-controlled,

post partum pain studies evaluated the effectiveness of a single dose of two 500-mg capsules (1,000 mg) to a single dose of two 325-mg tablets (650 mg) in 338 subjects. Two of the studies demonstrated that a single 1,000-mg dose was significantly more effective than a single 650-mg dose. One of the other studies failed to demonstrate a dose response between the two doses, and the last study failed to show separation of the active treatments from placebo. The overall safety profile for the 1,000-mg dose was similar to the 650-mg dose, with the exception of a higher incidence of dizziness. In 1975, FDA approved a 500-mg immediate-release tablet. Data from two crossover bioequivalence studies comparing two 500-mg capsules to two 500-mg tablets demonstrated the bioequivalence of the two formulations (Ref. 3).

The IAAA Panel further evaluated acetaminophen and recommended in its 1977 report (42 FR 35346) that acetaminophen be generally recognized as safe and effective. The IAAA Panel's evaluation of effectiveness was based on data from a number of controlled and uncontrolled studies of the effectiveness of a variety of acetaminophen doses, i.e., 300, 325, 330, 500, 600, 1,000, and 1,200 mg (42 FR 35346 at 35412). However, the IAAA Panel's evaluation did not include an assessment of the relative effectiveness of each of the dosage strengths. The Panel determined the maximum daily safe dosage to be not greater than 4 g in a 24-hour period. Upon publication of that document, FDA permitted OTC marketing without an NDA provided the product was consistent with the IAAA Panel's recommended labeling. FDA's 1988 TFM for OTC IAAA drug products proposed to include acetaminophen as a monograph ingredient (53 FR 46204 at 46255). FDA revised the IAAA Panel's recommended dosing regimens but maintained the maximum limit of 4 g in a 24-hour period.

To determine the maximum daily safe dosage (4 g of acetaminophen in a 24-hour period), the Panel reviewed numerous references that describe cases of serious liver damage associated with excessive use of acetaminophen (42 FR 35346 at 35413). Most of these cases were associated with single dose oral ingestions of greater than 15 g of acetaminophen. Based on this information, the Panel concluded that a single dose less than 15 g is not usually associated with serious liver injury. The Panel also noted that 15 g is 23 times the usual recommended dose of 650 mg and approximately 4 times the maximum recommended daily dose of 4 g. In estimating the safety margin, the Panel decided the comparison with the single dose (650 mg) was probably more appropriate than the comparison with the daily therapeutic dose (4 g). The current information on unintentional overdose suggests that the margin of safety may be less than originally determined. The data on liver failure presented by Dr. Lee at the September 2002 NDAC meeting and the adverse event reports in the FDA AERS data suggest daily doses less than 10 g, ingested on consecutive days, presents a risk for liver injury in some individuals.

FDA invites comment on whether there are subpopulations of individuals who are more susceptible to developing liver injury when taking acetaminophen. The dosing information included in the AERS cases of hepatotoxicity reported for acetaminophen suggest that the median daily dose is in the 5- to 6-g range. FDA recognizes, however, that dosing information in the AERS reports is sometimes inaccurate and is difficult to validate. The information in the AERS cases of hepatotoxicity is adequate to raise concerns that there may be subpopulations at risk for developing hepatotoxicity with doses lower than the currently labeled maximum daily dose of 4 g. If such subpopulations can be identified, the maximum daily dose of 4 g may no

longer be considered safe for those individuals and should be lowered. If the at risk subpopulations cannot be identified, or addressed through appropriate labeling, and cases of liver injury continue to be reported, FDA may reconsider whether the labeled maximum daily dose is still generally recognized as safe and effective for use in the general population.

B. Daily Dose Recommendation for Alcohol Abusers

Following publication of the IAAA TFM in 1988, FDA received a comment recommending that the maximum daily dose of acetaminophen be reduced from 4 to 2 g per day for alcohol abusers. The comment did not provide any data to support a reduced maximum daily dose. In June 1993, NDAC considered: (1) Identifying a population at risk in terms of alcohol consumption, e.g., people who rarely drink, social drinkers, or alcohol abusers, (2) whether the data are sufficient to support a reduced maximum daily dose for alcohol abusers, and (3) if yes, what the reduced maximum daily dose should be. NDAC found the data insufficient and was unable to recommend a reduced maximum daily acetaminophen dose for alcohol abusers.

At the September 19, 2002, NDAC meeting, FDA described cases of hepatotoxicity involving the use of prescription combination (narcotic/ acetaminophen) products (Refs. 6 and 7). Many of these cases involved people with a history of alcohol abuse. NDAC was unable to recommend a reduced maximum daily acetaminophen dose for alcohol abusers, because of a lack of specific data.

One drug manufacturer issued a ‘‘Dear Doctor’’ letter to inform health professionals about the September 2002 NDAC meeting (Ref. 72). The letter stated: ‘‘The NDAC proceedings may generate media interest and, as a result, people may contact you with questions about OTC pain relievers such as

acetaminophen.'' The letter summarized the existing data that support the safety of acetaminophen, including the statement: ''Prospective data indicate that chronic alcoholics can take recommended doses of acetaminophen up to 4,000 mg/day without risk of liver injury.'' The letter cited two references from the medical literature to support the statement (Refs. 73 and 74). The letter continued: ''Acetaminophen can be used safely, at recommended doses, by the occasional moderate consumer of alcohol.''

FDA has reviewed the two references (studies of hepatotoxicity of the therapeutic dose of acetaminophen in people with alcohol abuse, conducted by the same investigators). One (Ref. 73) is a full study report of 201 people (102 on acetaminophen and 99 on placebo). The other (Ref. 75) was an abstract describing a pilot trial with 60 people (30 each on acetaminophen and placebo). A full report of this study is not available (Ref. 75).

Both studies were randomized, double-blind, placebo-controlled clinical trials conducted in an alcohol detoxification center to evaluate the hepatotoxicity of maximum therapeutic dosing of acetaminophen in long-term alcoholic subjects. In both studies, the subjects were treated with the maximum therapeutic dose of acetaminophen (1g four times a day) for 2 days, followed by a 2-day observation. The results showed that acetaminophen treatment did not significantly increase serum ALT, Aspartate Aminotransferase (AST), and International Normalized Ratio (INR), as compared to the placebo control. The authors concluded that there was no evidence that the daily maximum therapeutic dose of acetaminophen caused liver injury in alcoholics. However, FDA finds the data insufficient to support this conclusion.

Neither study included an assessment of the quantity, frequency, and duration of alcohol use by the subjects. Alcoholic detoxification history and

information on alcohol-related disorders, including more specific hepatic evaluations (such as hepatic CYP2E1 p450 enzyme levels, glutathione levels, or biopsy), were not reported. That information would have enabled a better evaluation of chronic alcohol use and underlying alcohol-induced liver abnormalities. Subjects with AST and ALT higher than 120 IU/L were excluded from the study, so no evaluation of subjects with underlying liver damage evidenced by slight elevations of liver function tests could be assessed. Such subjects may respond differently than those with more substantial hepatic impairment. Other investigators have similarly criticized the studies (Refs. 76 and 77). Assessing the change in liver function tests after drug administration may not adequately support a conclusion that the drug is without risk of liver injury in this population. If subpopulations of chronic alcoholics are sensitive to lower doses of acetaminophen, this type of study would be inadequate to make any assessment of risk.

FDA also finds that a 2-day treatment period may be too short to deplete the lowered hepatic gluthianone capacity in alcoholic people. The 2-day regimen cannot be extrapolated into the recommended 10-day dosing regimen in OTC drug product labeling. One individual agreed, stating that the investigators gave no rationale for dosing acetaminophen for only 2 consecutive days while the drug is approved for 4 g/day for 10 consecutive days and commonly used for prolonged periods of time (Ref. 78). Further, the individual stated that the lack of elevation in liver enzyme values after only 2 days of acetaminophen lends little support to the authors' conclusion regarding its safety in alcoholic people. FDA's detailed assessment of these studies is on file in the Division of Dockets Management (Ref. 79).

FDA concludes that these studies do not provide reliable evidence that people with chronic alcohol use can safely take 4 g/day of acetaminophen, particularly for up to 10 days in accordance with OTC drug product labeling. Based on the data presented by Dr. Lee on liver failure, the experience in the University of Pennsylvania Hospital series, and data from the AERS database, FDA believes that alcohol users are a significant percentage of persons who develop severe liver injury. Acetaminophen products already have an alcohol warning to alert consumers of the risk for developing hepatotoxicity. It is important to determine whether the labeling should include a lower daily dose for chronic alcohol users. At this time, FDA is seeking both comments and data to support a specific dosage for acetaminophen as safe and effective in people who consume alcohol.

C. Combinations With Methionine or Acetylcysteine

FDA is currently evaluating different safety measures to reduce the relative risks for hepatotoxicity associated with the use of acetaminophen. Theoretically, one method might be to administer acetaminophen and N-acetylcysteine (NAC) together. NAC is a chemical produced by the body that enhances the production of the enzyme glutathione. A small portion of acetaminophen undergoes cytochrome P450-mediated N-hydroxylation to form N-acetyl-p-benzoquinoneimine (NAPQI, a toxic metabolite of acetaminophen). Liver toxicity from acetaminophen overdose depends in part on production of NAPQ to levels that exceed the ability of the normal hepatic detoxification pathway to eliminate NAPQ. Glutathione is produced predominantly in the liver and is an important detoxifier of NAPQ. In the event of acetaminophen overdose in people with enhanced activity of CYP 2E1 (alcoholics, or people using anticonvulsants), glutathione liver stores are depleted. One substrate for

glutathione synthesis is cysteine. NAC protects against liver damage in early acetaminophen poisoning by production of cysteine, a glutathione precursor. The administration of precursors of cysteine, such as NAC or methionine, may prevent depletion of glutathione and, thus, liver injury (Refs. 80 and 81).

Scientific data supports the efficacy of treating acute acetaminophen overdose with early administration of NAC (Refs. 82 through 85). To determine whether there is any usage data of acetaminophen with NAC or methionine for the purposes of prevention of liver toxicity, FDA examined the literature from 1975 to December 2002. FDA did not find any articles that specifically addressed whether either combination (when used at the therapeutic dose level) would prevent liver toxicity.

The UK is the only country where a combination product containing acetaminophen and methionine is available. The marketed product contains 500 mg acetaminophen and 100 mg methionine. One published study summarized the issues related to combining acetaminophen and methionine (Ref. 85). The authors acknowledge that there are no data available on the relative efficacy or the prophylactic antidotal dose of methionine for protecting the liver after acetaminophen overdose in humans.

At this time, FDA finds insufficient evidence that combinations of acetaminophen with NAC or methionine would prevent or reduce acetaminophen-induced liver toxicity. FDA seeks comments and data on this issue.

D. Package Size and Configuration Limitations

At the September 19, 2002, NDAC meeting, a representative from a national consumer organization reported that the UK implemented package size restrictions on acetaminophen. He noted that an early assessment of the

effect of the package size restrictions in the UK shows decreases in total and severe acetaminophen overdoses, as well as decreases in acetaminophen related toxicity leading to liver transplant or death. The representative did not provide any data to support his comments. FDA seeks comments on package size and package configuration limitations as a mechanism to increase safe use of acetaminophen products by reducing overdose. Comments should address the possible impact of such measures on unintentional and intentional overdose.

E. Label Warning for Individuals With Human Immunodeficiency Virus (HIV)

A citizen petition (Refs. 86 and 87) requested that FDA consider the need for a warning about the increased risk of liver injury from the use of acetaminophen by individuals infected with HIV. The request is based on the following reasoning:

- Glutathione (GSH) deficiency is frequent in HIV-infected individuals.
- Acetaminophen depletes GSH (essential for the detoxification of acetaminophen's toxic metabolite) and is potentially more toxic to GSH-deficient individuals.
- GSH deficiency is associated with impaired survival in persons with HIV disease, and acetaminophen may further reduce survival by depleting GSH.

In support of this request, the petitioner (Ref. 86) provided published studies of: (1) GSH and cysteine levels in plasma, peripheral blood monocytes and lymphocytes, and in the pleural fluid of HIV-positive individuals, and (2) the effects of GSH replacement in model systems and HIV-infected individuals. A subsequent submission (Ref. 87) provided a search of the worldwide literature that included studies of: (1) Nonhepatic GSH levels in numerous

disease states, (2) the effects of treatment with NAC or other GSH-replenishing drugs in diseases and conditions in which GSH is decreased, (3) the causes of GSH deficiency in persons with HIV disease, (4) an association between GSH deficiency and impaired survival in persons with HIV disease, and (5) the effect of NAC replacement therapy on clinical outcomes in persons with HIV disease.

A comment (Ref. 88) disagreed with the petitioner's assertions for the following reasons:

- The available data do not demonstrate that acetaminophen reduces total body or circulating GSH when taken as recommended.
- There currently are no studies that demonstrate that acetaminophen has any impact on the survival of HIV patients.
- The depletion of hepatic GSH that occurs after acetaminophen overdose is not related to plasma GSH levels.
- The source of plasma GSH in humans is not clearly defined.

FDA finds that although data from in vitro and in vivo studies (Refs. 89 through 96) have documented low levels of GSH and its precursors in HIV infection, the effect of this deficiency on survival has not been clearly established. Data from in vitro studies (Refs. 97 through 100) have demonstrated improvement in healthy and HIV-infected T-cell functioning post exposure to NAC. However, these findings have not been correlated with survival from in vivo studies. While some studies of the effects of NAC administration in HIV-infected individuals (Refs. 89, 90, and 101 through 104) have demonstrated an increase in GSH, the majority of studies were not designed to assess survival.

Herzenberg, et al. (Ref. 102) discussed results from several studies in HIV-infected patients that evaluated the relationship between GSH levels and survival, the administration of NAC in patients with low GSH levels in whole blood and in CD4 T cells, and the effect of NAC on survival in patients with low GSH levels in CD4 T cells. The presentation of data in the report made it difficult to understand the study design details. Other problems based on the information presented included: Survival data was not collected in a significant proportion of the population (17 percent), baseline characteristics of the individuals in all of the trials were not presented, the use of antiviral treatments and other medications before and during the studies was not provided, and NAC administration after 8 weeks was not randomized. In their conclusions, the authors recommend that excessive exposure to acetaminophen be avoided in HIV-infected individuals. The report references acetaminophen overdose leading to GSH deficiency as a basis to support their recommendation. However, it does not provide sufficient information suggesting that intermittent or short-term use presents a problem in HIV patients. FDA concludes that this report does not provide a sufficient basis to restrict that use of acetaminophen in patients infected with HIV.

Further, a search of FDA's AERS database for hepatic adverse events in HIV-infected individuals who took acetaminophen failed to identify any case reports which fit the search parameters, i.e., acetaminophen, HIV infection, and hepatotoxicity. Thus, there is no clinical evidence of toxicity or decrease survival that can be attributed to the recommended use of acetaminophen in HIV-infected individuals since GSH levels were never validated to predict survival.

Given these facts, FDA does not consider the current data a sufficient basis for a warning. However, the issues raised by the petition highlight the need for additional information or research to clarify whether acetaminophen poses additional risk for certain population subgroups (e.g., conditions in which GSH is reduced). Therefore, FDA invites the submission of data and comments on this issue.

F. Drug Interactions Between Acetaminophen and Warfarin

The labeling for a currently marketed warfarin-containing prescription drug product lists acetaminophen as a drug that can increase warfarin's anticoagulant effect (Ref. 105). A reciprocal warning is not currently included on the consumer labeling for any OTC drug products that contain acetaminophen. To evaluate the need for a consumer warning regarding co-administration of warfarin-containing drugs with acetaminophen, FDA considered postmarketing adverse event case reports in our AERS database, studies published in the worldwide literature (Refs. 106 through 125), and three consultative reviews (Ref. 126, 127, and 128).

In the consultative reviews, FDA epidemiologists identified a cumulative total of 20 (3 probable and 17 possible) postmarketing adverse event case reports of prolongation of laboratory tests that monitor the ability of the blood to clot. These tests are the INR or Prothrombin Time (PT). These reports occur in individuals treated chronically with warfarin who concomitantly took acetaminophen and had minor or severe bleeding events. Of note, the only background characteristics that were identifiable in these case reports were that the individuals involved were generally elderly, had been on stable anticoagulant therapy for a prolonged period of time (several months to years), and used acetaminophen ''regularly'' instead of ''intermittently'' for

approximately 3 to 14 days prior to the discovery of their abnormally prolonged INR or PT. The dosages of acetaminophen reportedly ingested by these individuals ranged from 1.2 to 4.5g/day. FDA's epidemiologists attribute the small number of postmarketing case reports collected to underreporting. We believe that the actual number of cases is much higher, based on the numbers of people who are treated with anticoagulant therapy.

FDA's epidemiologists also conducted two literature searches on this topic. In the first (Ref. 126), FDA reviewed 11 published articles describing three double-blind, placebo-controlled, randomized studies that demonstrated a prolongation of warfarin's anticoagulant effect when acetaminophen was used concomitantly in a chronic manner (Refs. 110, 112, and 113). Two additional published double-blind, crossover studies showed that people on a stable warfarin dose who were acutely dosed with acetaminophen did not experience any changes in their anticoagulant status (Refs. 111 and 117). A prospective, case-control study looked at a cohort of people from an anticoagulant clinic, each of whom were noted to have an INR greater than 6 on a routine followup clinic visit. The study found that after controlling for other risk factors associated with prolongation of anticoagulant status (i.e., medication use, recent diet, illness, alcohol consumption, and actual warfarin use), the use of acetaminophen was an independent dose-dependent risk factor for having an INR over 6 (P-value for trend <0.001). Other independent variables associated with the development of a prolonged INR were identified and included: Advanced malignancy (odds ratio [OR], 16.4; 95 percent confidence interval [CI], 2.4 to 111.0), recent diarrheal illness (OR, 3.5; 95 percent CI, 1.4 to 8.6), decreased oral intake (OR, 3.6; 95 percent CI, 1.3 to 9.7), ingesting a higher dose of warfarin than prescribed (OR, 8.1; 95 percent

CI, 2.2 to 30.0), and taking new medications known to interact with warfarin (OR, 8.5; 95 percent CI, 2.9 to 24.7) (Ref. 113). The validity of this study's findings was subsequently questioned when it was publicly criticized in the literature for its flawed methodological design, such as the overlapping of risk factors in the population studied (i.e., fever and the use of acetaminophen), and the lack of reported adverse events (Refs. 115, 116, and 118). Additionally, the mechanism by which a possible acetaminophen-warfarin interaction occurs has yet to be clearly identified (Refs. 119 and 120).

The second updated literature review (Ref. 127) noted two additional case controlled studies generated from patient cohorts followed in anticoagulation clinics that were published in the European literature (Refs. 123 and 124). Both of these studies failed to document the existence of a possible drug-drug interaction in stable anticoagulated people treated with the warfarin analogues phenprocoumon or acenocoumarol and using acetaminophen concomitantly.

The data generated from the literature searches are conflicting. Although many of the studies controlled for other variables known to potentate warfarin's anticoagulant effect, it is not known if they all also controlled for life style factors such as diet, the use of vitamins and herbal medications, physical activity, concurrent illness, or liver status. Extrapolating the clinical findings generated from the study by Fattinger, et al. may not be applicable to real life situations, since this trial was conducted in people where background life style factors such as diet and physical activity did not come into play due to the controlled study environment (Ref. 124). The study by van den Bemt, et al. may have also failed to demonstrate the existence of an adverse drug-drug interaction associated with the concomitant use of acetaminophen with either of the warfarin analogues phenprocoumon or

acenocoumarol, because these drugs may be metabolized differently than warfarin (Ref. 123). FDA believes that the current available data do not demonstrate sufficient evidence to warrant a consumer warning for warfarin-acetaminophen interaction. However, we are seeking comments or data on whether additional labeling about this drug-drug interaction is warranted at this time.

VIII. Legal Authority

A. Statement About Warnings

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act (the act). This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter* v. *Novartis Pharmaceuticals Corp.*, 252 F. 3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see the final rule on ''Labeling of

Diphenhydramine-Containing Drug Products for Over-the Counter Human Use'' (67 FR 72555, December 6, 2002).

B. Marketing Conditions

This proposal applies to all OTC internal analgesic/antipyretic drug products that contain an ingredient included in proposed § 201.325(a). Upon issuance of a final rule, any new labeling will apply to any product that is initially introduced or initially delivered for introduction into interstate commerce. Such products would be misbranded under section 502 of the act (21 U.S.C. 352) and would be subject to regulatory action unless:

- Products marketed without an NDA include the required labeling within 12 months after any final rule that is issued based on this proposal.
- Products marketed with an NDA include the required labeling within 12 months after any final rule that is issued based on this proposal. The labeling may be put into use without advance FDA approval provided it includes the information described in the final rule. Manufacturers should submit a supplement under § 314.70(c).

If companies voluntarily implement the labeling in this proposal before a final rule issues, FDA intends to provide those companies 18 months to implement the labeling in the final rule.

IX. Voluntary Implementation

The labeling proposed in this document represents a change from the current labeling required for OTC IAAA drug products. Although FDA considers these proposed labeling changes to be very important, holders of approved NDAs for OTC IAAA drug products will not be required to implement the proposed labeling at this time. However, holders of approved NDAs for these drug products may implement the proposed labeling without

advance FDA approval provided the labeling includes the information in proposed § 201.325. A supplement must be submitted under § 314.70(c) to provide for the implementation of such labeling. The supplement and its mailing cover should be clearly marked: ''Special Supplement—Changes Being Effected.''

FDA considers the proposed labeling in this document to be important to the safe use of OTC IAAA drug products and strongly encourages manufacturers of these products to voluntarily implement the proposed labeling changes before FDA issues a final rule. However, voluntary compliance with the proposed labeling in this document is subject to the possibility that FDA may revise the wording of some of the proposed statements or changes, or not require the statement or change, as a result of comments filed in response to this proposal. Because FDA wishes to encourage the voluntary use of the proposed labeling statements and changes, FDA advises that manufacturers will be given 18 months after publication of a final rule to use up any labeling implemented in conformance with this proposal (see section XV of this document).

X. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule may have a significant

economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million or more (adjusted annually for inflation) in any one year.''

FDA tentatively concludes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order. As discussed in this section, FDA has tentatively determined that this proposed rule will not have a significant economic impact on a substantial number of small entities. Because the rule does not impose any mandates on state, local or tribal governments, or the private sector that will result in an expenditure in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act. The current threshold after adjustment for inflation is about $110 million.

FDA estimates that manufacturers and marketers of OTC IAAA drug products would incur one-time compliance costs of $32 million in the first year to revise labeling to conform to the proposed rule. The benefits of this proposed rule are based on estimated annual reductions from 1 to 3 percent in serious illnesses and related hospital and emergency room costs and in deaths related to unintentional overdosing. If 1 to 3 percent of these adverse events are avoided, the monetized benefits would be $6 million to $17 million

per year, respectively. The present value of the monetized benefits over a 10-year period is $41 million to $126 million assuming a 7-percent discount rate,[1] and $49 million to $147 million at a 3-percent discount rate. If we assume only a 1 percent reduction in the illnesses and fatalities analyzed, the benefits of this proposed rule outweigh the costs. We summarize the impacts in Table 10 of this document.

FDA notes that we lack the data needed to confidently predict a percent reduction in serious cases related to unintentional overdosing. Because of the uncertainty in these estimates, we estimated an annual average number of adverse events that would need to be avoided over a 10-year period to reach a breakeven point. Social benefits would equal the costs of compliance if the proposed rule prevented about 1 fatality each year (0.9 and 0.7 fatalities over 10 years at a 7-percent and a 3-percent discount rate, respectively). Alternatively, if no fatalities are avoided, the proposed rule would need to prevent about 475 hospitalizations per year over the 10-year period at a 7-percent discount rate. At a 3-percent discount rate, an average reduction of 410 hospitalizations per year is needed.

TABLE 10.—SUMMARY OF IMPACTS

Benefits:	($ Million)
Monetized 1 and 3-percent reduction in illnesses and mortality, per year	$5—$17
Present value over 10 years at 7 percent	$41—$126
Present value over 10 years at 3 percent	$49—$147
Costs:	($ Million)
One-time label revision, first year	$32

A. Need for the Rule

In September 2002, FDA's NDAC recommended changes to the labeling of OTC IAAA drug products to better inform consumers about the active ingredients and possible side effects caused by improper use. Although FDA

[1]Per the Office of Management and Budget (OMB) Circular A4, revised in 2003.

considers acetaminophen to be safe and effective when labeled and used correctly, taking too much can lead to liver damage and death. Similarly, the use of NSAIDs can lead to GI bleeding and renal toxicity. The number of cases of injury reported is a very low percentage of the total use of OTC acetaminophen and NSAID drug products. For many people, the risks are quite low because they use these products only occasionally. The risks may be greater for people who use these products more frequently and/or do not follow the labeling information on the package. The risk of injury may be increased for certain populations and under certain conditions of use.

There are multiple reasons for unintentional acetaminophen overdoses. First, acetaminophen is an active ingredient in a wide variety of both OTC and prescription drug products. For prescription products, the immediate prescription container may not state that the product contains acetaminophen or state the maximum daily dose limit. Consumers may often fail to recognize the presence and amount of acetaminophen ingredients in OTC and prescription drug products. This lack of knowledge can result in a person taking two different products containing acetaminophen simultaneously. Moreover, many consumers are unaware that exceeding the recommended dosage for acetaminophen can lead to unintentional overdosing and cause potential harm. Based on the evidence discussed in this document, FDA finds that there is sufficient incidence of liver damage associated with acetaminophen to warrant new labeling, and that without the new labeling, acetaminophen products would no longer be considered generally recognized as safe and effective and not misbranded for OTC use.

Results of several large-scale clinical studies performed in the United States and in other countries have established that the use of NSAIDs is an

important risk factor for serious GI adverse events, especially bleeding. The risk is higher for certain populations. Based on the evidence discussed in this document, FDA further finds that NSAIDs increase the risk for GI adverse events and that without a new stomach bleeding warning in the labeling for aspirin and other NSAIDs the products would no longer be considered generally recognized as safe and effective and not misbranded for OTC use.

The purpose of this proposed rule is to amend FDA's OTC drug labeling regulations and the TFM for OTC IAAA drug products to include new warnings and other labeling requirements to advise consumers of potential risks and when to consult a doctor. FDA is also proposing to remove the alcohol warning in § 201.322 and incorporate new alcohol-related warnings and other labeling for all OTC IAAA drug products. FDA is proposing certain warning information targeted to age specific populations. In addition, FDA is proposing that the presence of acetaminophen or any NSAID would appear prominently on the products' PDP. Table 11 presents an overview of the proposed changes by type of product.

TABLE 11.—OVERVIEW OF THE PROPOSED LABEL CHANGES BY PRODUCT TYPE

Type of Product	Proposed Change
Acetaminophen	Add a new warning to include information on serious liver injury. Include the name acetaminophen [highlighted or in bold type, and in a prominent print size] on the PDP.
NSAIDs (e.g., aspirin or ibuprofen)	Add a new warning to include information on stomach bleeding. Include the name of the NSAID ingredient [highlighted or in bold type] on the PDP. Include the word ''(NSAID)'' [highlighted or in bold type, and in a prominent print size] on the PDP either as part of the established name of the drug or after the general pharmacological (principal intended) action of the NSAID ingredient.
Combination products containing acetaminophen or an NSAID and a nonanalgesic ingredient	Include the name acetaminophen or the name of the NSAID ingredient [highlighted or in bold type, and in a prominent print size] and the names of the other active ingredients on the PDP. Products containing an NSAID ingredient must include the word ''(NSAID)'' as stated under NSAIDS.
All IAAA drug products	Remove the current alcohol warning in § 201.322, and incorporate new alcohol-related warnings format. For a specific period of time, add to the PDP the statement ''See new warnings information''. We are proposing that this statement appear highlighted in the same way that the name ''acetaminophen'' or the presence of an NSAID appear on the PDP. The statement would appear highlighted (e.g., fluorescent or color contrast) or in bold type; and be in one of the following sizes, whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2).

B. Impact of the Rule

FDA contracted with Eastern Research Group, Inc. (ERG) to assess the costs and benefits of this proposed rule. The following is a summary of ERG's analysis; the full report, including details on assumptions, cost calculations, and findings, is on file in the Division of Dockets Management (Ref. 129).

Manufacturers and marketers of OTC IAAA drug products would incur one-time costs to revise affected product labeling to comply with the proposed labeling changes. We assumed an implementation period of 12 months for one-time costs for a major labeling revision. We estimated one-time costs for a major labeling revision using a pharmaceutical labeling revision cost model. This labeling model is described in detail in Appendix A of the ERG report (Ref. 129).

To develop the original model, FDA and ERG interviewed pharmaceutical representatives from regulatory, legal, manufacturing controls, and labeling departments to collect information on labeling change cost components, type of personnel affected, and costs. The model incorporates data on average industry costs by company size, including, where applicable, modifications to packaging configurations. Industry consultants also provided information on model inputs related to the OTC IAAA industry, the labeling revision process, the costs of modifying labeling, and the frequency of packaging reconfiguration changes.

The baseline for this proposed action is full compliance with the format and content requirements for OTC drug product labeling in 21 CFR 201.66. In the final rule that established these requirements on March 17, 1999 (64 FR 13254), FDA accounted for the total incremental costs to comply with requirements, including 6.0 font size and related costs for increased package

size and longer labeling where applicable. FDA notes that although some forms of packaging (for small quantities) have been granted extensions on compliance dates, many packaging alternatives now exist to assure compliance.

Manufacturers routinely change labels at varying intervals and have standardized procedures in place for complying with FDA requirements. The analysis assumes that one-half of the manufacturers of OTC IAAA drug products typically redesign their label every 2 years, the remainder every 3 years, based on consultant input. For this analysis, ERG assumed that manufacturers whose label redesign cycle is less than the implementation period will not incur any regulatory costs. For example, if a company routinely revises its product labeling annually and is given at least that long to incorporate the required changes, ERG judged that the regulatory revision can be made at essentially no cost.

The costs of labeling change depend on the type of labeling (e.g., carton and container label) and whether there is sufficient labeling space to accommodate the proposed changes. There are an estimated 22,500 OTC IAAA drug product stockkeeping units (SKUs), split evenly among branded and private labels, according to an industry consultant.[2] FDA assumes branded SKUs are distributed by firm size: 50 percent small, 17 percent medium, and 33 percent large. Based on consultant input, we assumed the distribution of SKUs among OTC IAAA drug products as follows: Acetaminophen, 45 percent; NSAIDS (except ibuprofen), 38 percent; ibuprofen, 15 percent; and combinations of IAAAs (i.e., contain acetaminophen and aspirin), 2 percent. Cost estimates are for small, medium, and large branded companies, private

[2]Estimates of affected SKUs are 18,000 (CDER) and from 20,000 to 25,000 (per industry consultant). This number of SKUs includes products marketed by manufacturers, repackers, relabelers, and distributors.

label companies, and by affected product group. The ERG report presents model assumptions and methods for calculating costs.

ERG visited five stores—two major chain drug stores and three convenience stores—to collect information on the distribution of types of OTC IAAA drug product packaging. Roughly 80 percent of OTC IAAA drug products were packaged in cartons and 20 percent in containers. To assess the increase in label space requirements, ERG purchased 45 affected products, with an emphasis on smaller packages.

1. Label Area Changes

ERG collected and recorded descriptive packaging information on the sampled products and measured existing font size, labeling area and labeling text on packages, and the area needed for replacement text. ERG then calculated the percentage increase in square millimeters (mm^2) needed to accommodate the proposed labeling changes. In all cases, ERG determined that the requirement to add active ingredient names on the PDP, while requiring major redesign in some cases, did not impose a change in the size of the PDP or the addition of non-standard labeling (such as adding a fifth carton panel or peelback label). ERG estimates that the increase in existing label area needed to accommodate the additional proposed label warnings and text ranges from 8 percent (acetaminophen) to 32 percent (ibuprofen).

2. Package size or type changes

ERG measured the available panels and white space on the 45 packages sampled. If the available white space was greater than the estimated increase in space necessary to accommodate the new label warnings, ERG determined the product would not require an increase in carton or container size. Based on this review, ERG assumed that all current packaging can accommodate the

required changes in this proposal without altering label sizes, package sizes, or adding non-standard labels. Therefore, ERG did not assign costs for adjustments to packaging. Although finding only a few small foil packs that did not comply with the OTC Drug Facts labeling requirements, ERG noted that alternative types of packaging are now available to replace the older packages.

Table 12 presents the estimated total and annualized costs of compliance with the OTC IAAA drug product proposed rule. The total estimated one-time costs to revise labeling are $32.6 million. The estimated annualized cost over the relevant relabeling period is $15.2 million at a 7-percent discount rate. The estimated average annualized cost per SKU is $677 ($15.2 million/22,500 SKUs).

TABLE 12.—ESTIMATED TOTAL AND ANNUALIZED COSTS OF COMPLIANCE ($ MILLION)

	Product Type				
	Company Type	Acetaminophen	NSAID (except Ibuprofen)	Ibuprofen	Combinations of IAAAs
Small Brand	2.2	1.8	0.7	0.1	4.9
Medium Brand	2.1	1.8	0.7	0.09	4.7
Large Brand	6.0	5.1	2.0	0.3	13.3
Private Label	4.4	3.7	1.5	0.2	9.7
Total	14.7	12.4	4.9	0.7	32.6
Total Annualized Costs (at 7-percent discount rate)					
Small Brand	1.0	0.9	0.3	0.05	2.7
Medium Brand	1.0	0.8	0.3	0.04	2.2
Large Brand	2.8	2.4	0.9	0.1	6.2
Private Label	2.0	1.7	0.7	0.09	4.5
Total	6.9	5.8	2.3	0.3	15.2

C. Impact on Affected Sectors

Manufacturers of OTC drug products are classified in North American Industry Classification System (NAICS) 325412, pharmaceutical preparation manufacturing. This classification code includes all manufacturers of

prescription and OTC pharmaceutical preparations, but does not include relabelers, repackers, and distributors. The Small Business Administration (SBA) defines a small business in this industry classification code as one with fewer than 750 employees. In NAICS 325412, over 90 percent are considered small entities. The affected industry is a subset of the OTC pharmaceutical industry. This proposed rule affects an estimated 258 manufacturers (of which 200 are small) of OTC IAAA drug products.

Manufacturers often package private label products, although some chains package their own brands. SBA considers the following to be small: (1) Any pharmacy or drug store with annual sales under $6 million, and (2) supermarkets and other grocery stores and warehouses and superstores with sales under $23 million. Generally, only the largest supermarket and drug store chains (263 firms) or superstores (9 firms) would have their own private label. ERG included only those largest retail chains with annual sales of $100 million or more as having their own private labels. Thus, FDA believes that there are no small entities in these retail sectors that are affected. Marketers of private label OTC drug products are classified as follows:

NAICS 446110, Pharmacies and drug stores

NAICS 445110, Supermarkets and other grocery stores

NAICS 452910, Warehouse clubs and superstores.

Packaging and labeling services that contract with pharmaceutical manufacturing firms may also be affected, but we assume manufacturers bear the costs of any labeling changes. Both the manufacturing and marketing sectors will most likely share costs, but the extent is not known. Therefore, this impact analysis first assumes that manufacturers absorb all of the labeling

costs. We then assume that all private labeling costs are absorbed by chain stores and calculate impacts.

To assess the impact on entities in the pharmaceutical-manufacturing sector (NAICS 325412), ERG adjusted SBA data on firm size and revenues to estimate average receipts per firm for the affected sector. ERG applied modeling assumptions to estimate the number of large and small affected firms. ERG further assumed the distribution of all 22,500 affected SKUs is one-third for large firms (producing either branded or private label products) and two-thirds for small firms. To estimate the share of total compliance costs for each size category, ERG distributed the SKUs attributed to small businesses in the same proportion as employment. The distribution of SKUs determines the distribution of compliance costs by employment size category. Table 13 summarizes the estimated impacts for pharmaceutical manufacturers, the total cost per firm based on $677 per SKU, and the compliance costs as a percent of revenues.

TABLE 13.—ESTIMATED IMPACTS ON PHARMACEUTICAL PREPARATION MANUFACTURING FIRMS BY SIZE (NAICS 325412)

Employment Size	Average Receipts per Firm ($mil)	Assumed No. of SKUs	SKUs per Firm	Total Firm Cost ($000)[1]	Compliance Cost as % of Receipts
<20	1.7	841	9	6.0	0.340%
20–99	12.2	2,591	65	43.8	0.361%
100–499	61.9	5,506	148	100.2	0.162%
500–749	366.8	6,062	225	151.9	0.041%
Total Small	29.1	15,000	75	50.8	0.175%
>750	947.8	7,500	130	88.1	0.009%
Total	109.6	22,500	87	59.1	0.054%

[1]Number of SKUs x $677 per SKU.
Source: SBA, 1999 and ERG estimates.

Total estimated compliance costs per firm ranged from $6,000 for firms with fewer than 20 employees to $152,000 for firms with 500 to 749 employees. The compliance cost as a percent of receipts is less than 1 percent for all firms; 0.18 percent for all small firms and 0.01 for large firms. This estimate of impacts is somewhat understated because the census data used to derive

estimates includes both OTC and prescription drug manufacturers. However, no alternative revenue and employment size information for affected product lines is available. We tentatively conclude that this estimate of the impacts of the proposed rule does not constitute a significant economic impact on a substantial number of small entities.

In a similar analysis, we assume chain stores absorb costs for all 11,250 private label SKUs. Compliance costs as a percent of receipts are less than 0.001 percent for all of the affected sectors: Pharmacies, drug stores, superstores, supermarkets, and other grocery stores. No small entities are affected.

Manufacturers routinely change labels at varying intervals and have standardized procedures in place for complying with FDA requirements. The proposed rule would not require any new reporting and record keeping activities and no additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with the proposed rule; FDA is proposing to remove the existing alcohol warning in § 201.322.

D. Alternatives

FDA does not believe that there are any alternatives to the proposed rule that would adequately provide for the safe and effective use of OTC drug products containing IAAA active ingredients. Nonetheless, FDA considered but rejected the following alternatives: (1) Not adding the new information to OTC IAAA drug product labeling, and (2) a longer implementation period. FDA does not consider either of these approaches acceptable because they do not assure that consumers will have the most current labeling information needed for the safe and effective use of these products. FDA considers this proposed rule the

least burdensome alternative that meets the public health objectives of this rule.

E. Benefits

FDA's proposed requirements are intended to enhance consumer awareness and knowledge of the active ingredient in OTC IAAA drug products. These new proposals include:

- New label warnings
- Age specific information
- Advising consumers of potential risks and when to consult a doctor
- Prominent display of active ingredients on the PDP

The revised alcohol statements are intended to provide clearer warnings to high-risk individuals about product use. The overall intent of these proposed requirements is to reduce the liver damage and GI bleeding episodes that occur due to unintentional overdosing with these drugs. The proposed requirements are also intended to reduce the incidence of adverse health outcomes among high-risk subpopulations consuming proper doses of OTC IAAA drug products (e.g., people with liver disease or prone to GI bleeding).

To estimate the benefits of this proposed rule, we developed baseline information on the frequency of hospitalizations, emergency room visits, and deaths related to unintentional overdosing with OTC IAAA drug products. We used a value of $5 million to represent the premature loss of a statistical life in previous analyses (see 66 FR 6137, January 19, 2001). We quantified the related hospital and emergency room costs, estimated related morbidity costs, applied a value of $5 million to the premature loss of a statistical life, and estimated annual savings if 1 to 3 percent of these adverse events and deaths are avoided (Ref. 129).

We lack evidence to predict with certainty a specific level of reduction in adverse events. Nonetheless, we believe that presenting consumers with improved label warnings and more prominently displaying the active ingredients on the PDP will promote safer use of OTC IAAA drug products. Specifically, prominent display of the active ingredients on the PDP would alert consumers to the presence of the active ingredients in OTC IAAA drug products and help minimize the risks of unintentional overdosing. The revised warnings are intended to assist consumers, including higher risk individuals, to use OTC IAAA drug products more safely and lead to at least a modest reduction in unintentional overdosing.

Table 14 summarizes the baseline and estimates of the number of avoidable hospitalizations and emergency room visits, the average cost per case, and potential savings from events avoided. These data do not include reported cases of intentional overdosing. Based on the total monetized costs per adverse health outcome and the number of cases estimated to be avoided each year (from 1 to 3 percent), the total monetized benefits of illness avoided range from $0.6 million to $1.8 million per year ($592,600 to $1,777,900).

TABLE 14. —SUMMARY OF ANNUAL MONETIZED BENEFITS OF ILLNESSES AVOIDED ASSOCIATED WITH THE PROPOSED RULE (2001 $)

Adverse Health Event	Hospital Costs	Willing to Pay to Avoid Illness	Total Monetized Value of Illness Avoided	Potentially Preventable Baseline Cases per Year(1)	Annual Number of Cases Avoided Due to Proposed Rule(2)	Total Annual Monetized Benefits of Illness Avoided ($000)
Minor drug toxicity or emergency room visits	$209	$301	$510	3,380	34–101	$17.2–$51.7
Acetaminophen poisoning episode with hospitalization	$8,579	$2,000	$10,579	3,424	34–103	$362.2–$1,086.8
NSAID poisoning episode with hospitalization	$8,579	$357	$8,936	2,269	23–68	$202.8–$608.3
Acute renal failure with hospitalization	$22,251	Not Estimated	$22,251	5	0.05–0.15	$1.1–$3.3
Acute renal failure with dialysis	$22,251	Not Estimated	$22,251	0.7	0.007–0.021	$0.2–$0.5
GI bleeding	$14,653	$357	$15,010	61	0.6–1.8	$9.2–$27.5
Total monetized benefit of illness avoided	NA	NA	NA	NA	NA	$592.6–$1,777.9

(1) The number of potentially preventable baseline cases per year is derived from data on emergency department and hospital cases of overdosing, poisoning, or other serious adverse outcomes associated with acetaminophen and NSAID use, adjusted to estimate only unintentional cases.
(2) Assumes this proposed rule would reduce annual adverse event cases by 1 to 3 percent.
Source: FDA Section III.B.2 of this document and ERG report (Ref. 129).

In addition to estimating the value of preventing adverse drug events that result in emergency department or hospitalization, we consider the annual number of deaths related to unintentional acetaminophen overdoses. FDA estimates that from 1996 to 1998, an annual average of 99 adult deaths were related to unintentional acetaminophen overdoses (see section III.B.2 of this document and the ERG report (Ref. 129)). We assume the proposed rule would reduce fatalities by 1 to 3 percent annually. Applying a value of $5 million for each fatality prevented, we estimate the total benefits associated with preventing 1 to 3 fatalities to be $5 to $15 million annually ($2001).

If the proposed improved labeling and warnings reduced serious adverse events by 1 to 3 percent each year, the total monetized value of preventing illness and fatalities because of improved labeling and warnings would be $5.6 million to $16.8 million per year, respectively. These benefits are presented in 2001 dollars.

Benefit Cost Comparison. Industry would incur the one-time costs of the proposed rule of $32.6 million in the first year. In 2001, the costs were $32.0 million. However, the estimated savings from reduced hospital costs and deaths avoided, from $5.6 to $16.8 million, would accrue each year. Over a 10-year period, the $5.6 to $16.8 million per year in benefits has a present value of $41.2 to $126.1 million at a discount rate of 7 percent, and a present value of $49.1 to $147.4 million at a discount rate of 3 percent. Thus, the benefits of this proposed rule, assuming a 1-percent reduction in current levels of adverse health outcomes associated with the use of OTC IAAA drug products, will more than offset the costs of the proposed rule. Table 15 summarizes the estimated benefits and costs of this proposed rule.

TABLE 15.—SUMMARY OF IMPACTS

Benefits/Costs	($Million)
Benefits:	
Monetized 1 and 3 percent reduction in illnesses and mortality, per year Present value over 10 years at 7 percent Present value over 10 years at 3 percent	$5.6–$16.8 $41–$126 $49–$147
Costs:	
One-time label revision, first year	$32.6

Break-even Analysis. FDA notes that we lack the data needed to confidently predict a percent reduction in serious cases related to unintentional overdosing. Because of the uncertainty in these estimates, we estimated an annual average number of adverse events that would need to be avoided over a 10-year period to reach a breakeven point (i.e., the cost of compliance/present value of avoiding one death each year for 10 years). The proposed rule would need to prevent about 1 fatality each year over 10 years [0.9 fatality ($32/$37.6 million at a 7-percent discount rate) and 0.7 fatality ($32/$43.9 million at a 3 percent discount rate)]. Alternatively, if no fatalities are avoided, the proposed rule would need to prevent about 476 hospitalizations ($32 million/$67,000) each year over the 10-year period. This estimate uses the present value of the lowest benefit category of poisoning episode with hospitalizations, $8,936 per episode over 10 years at a 7-percent discount rate. At a 3 percent discount rate, an average of 407 hospitalizations ($32 million/$79,000) would need to be avoided annually over the period.

Although we lack evidence to predict with certainty a specific level of reduction in adverse events, if we assume only a 1-percent reduction in the illnesses and fatalities analyzed, the benefits of this proposed rule outweigh the costs. FDA finds that this proposed rule will enhance public health and promote the safer use of OTC IAAA drug products.

This economic analysis, together with other relevant sections of this document, serves as FDA's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

FDA invites public comment regarding any significant economic impact that this rulemaking would have on affected manufacturers of these OTC IAAA drug products. Comments regarding the impact of this rulemaking should be accompanied by appropriate documentation. FDA is providing 150 days from the date of publication of this proposed rule in the **Federal Register** for comments on this subject to be developed and submitted. FDA will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to any final rule.

XI. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling statements are public disclosures of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public (5 CFR 1320.3(c)(2)).

XII. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this proposed action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule,

if finalized as proposed, would have a preemptive effect on State law. Section 4(a) of the Executive Order requires agencies to ''construe* * *a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.'' Section 751 of the Federal Food, Drug, and Cosmetic Act (act) (21 U.S.C. 379r) is an express preemption provision that applies to nonprescription drugs. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that:

* * no State or political subdivision of a State may establish or continue in effect any requirement— * * * (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.). * * *

Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See section 751(b), (c), (d), and (e) of the act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.) This proposed rule, if finalized as proposed, would amend the labeling for over-the-counter IAAA drug products to include new warnings and other labeling requirements advising consumers about potential risks and when to consult a doctor. Although any final rule would have preemptive effect, in that it would preclude States from issuing requirements related to the labeling of IAAA drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule, this preemptive effect is

consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both state legislative requirements and state common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise. See *Geier* v. *American Honda Co.*, 529 U.S. 861 (2000).

FDA believes that the preemptive effect of the proposed rule, if finalized as proposed, would be consistent with Executive Order 13132. Section 4(e) of the Executive Order provides that ''when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.'' FDA is providing an opportunity for State and local officials to comment on this rulemaking, and will conduct outreach to State and local governments or organizations representing them.

XIV. Request for Comments

In addition to requesting general comments on the proposal and the economic analysis, we are seeking comment on the following specific issues identified in the description of the proposed rule (presented here for the convenience of the reader):

1. Both comment and data on whether adult NSAID products should contain a warning regarding fluid loss or dehydration similar to children NSAID products (see section V.B.2 of this document).

2. Appropriate approaches to reduce unintentional acetaminophen overdose (see section VII.A of this document).

3. Whether more specific directions, such as those currently required for OTC drug products containing ibuprofen, should be considered for acetaminophen (see section VII.A of this document).

4. Both comment and data on whether there are specific populations of people for whom the maximum daily dose for acetaminophen is not safe and effective and should be lowered (see section VII.A of this document).

5. Both comment and data on specific dosage for safe and effective use of acetaminophen in people who consume alcohol (see section VII.B of this document).

6. Both comment and data on whether combinations of acetaminophen with NAC or methionine would prevent or reduce acetaminophen-induced liver toxicity (see section VII.C of this document).

7. Both comment and data on package size or package configuration limitations on the sale of acetaminophen (see section VII.D of this document).

8. Both comment and data on whether acetaminophen poses additional risk for certain population subgroups (e.g., conditions in which GSH is reduced) (see section VII.E of this document).

9. Both comment and data on whether additional labeling is necessary regarding acetaminophen-warfarin drug-drug interaction (see section VII.F of this document).

10. Comment on the proposal to include a warning on acetaminophen products for patients with liver disease to ask their doctor for advice. Also, request information and data on the current dosing practices of health providers who treat patients with underlying liver disease.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or three hard copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of

this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

XV. Proposed Effective and Compliance Dates

Because of the importance of the proposed labeling to the safe use of OTC IAAA drug products, FDA is proposing that any final rule that may publish based on this proposal become effective 12 months after its date of publication in the **Federal Register**. Manufacturers who voluntarily implement the labeling included in this proposal before the final rule is published will have 18 months after the date of publication of the final rule in the **Federal Register** to be in compliance with that final rule.

XVI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**), under Docket No. 1977N–0094L, unless otherwise indicated, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. Comment No. C1, Docket No. 1977N–0094I (formerly Docket No. 77N–094I).

2. Comment No. C2, Docket No. 1977N–0094I (formerly Docket No. 77N–094I).

3. FDA background information for September 19–20, 2002, NDAC meeting, *http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882b1.htm*.

4. NDAC meeting September 19–20, 2002 transcript, *http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T1.htm*. and *http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T2.htm*.

5. Additional information submitted for consideration at the NDAC meeting September 19–20, 2002.

6. Lee, W. M., ''Acute Liver Failure in the USA: Results of the US ALF Study Group,'' September 19, 2002 NDAC meeting transcript, *http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T1.htm* and slides *http://www.fda.gov/ohrms/dockets/ac/02/slides/3882S1_04_Lee_files/frame.htm*.

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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 343

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 201 and 343 (as proposed in the **Federal Register** of November 16, 1988 and August 21, 2002) be amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360g–360s, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Section 201.66 is amended by revising paragraph (c)(5)(ii)(E) to read as follows:

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

* * * * *

(c) * * *

(5) * * *

(ii) * * *

(E) Liver warning set forth in § 201.325(a)(1)(iii) and/or stomach bleeding warning set forth in § 201.325(a)(2)(iii). The liver warning shall follow the subheading ''Liver warning:'' and the stomach bleeding warning shall follow the subheading ''Stomach bleeding warning:''

* * * * *

§ 201.322 [Removed]

3. Section 201.322 is removed.

4. Section 201.325 is added to subpart G to read as follows:

§ 201.325 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required warnings and other labeling.

(a) *Labeling*. The labeling for all over-the-counter (OTC) drug products containing any internal analgesic/antipyretic active ingredients (including, but not limited to, acetaminophen, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate) alone or in combination must bear the following labeling in accordance with §§ 201.60, 201.61, and 201.66.

(1) *Acetaminophen*.

(i) *Principal display panel*. The presence of ''acetaminophen'' in the product must be prominently stated on the principal display panel (PDP), as defined in § 201.60.

(ii) *Statement of identity*. The statement of identity appears in accord with §§ 201.61, 299.4, and 343.50(a) of this chapter. The ingredient name acetaminophen must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes,

whichever is greater: (1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or (2) at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2). The presence of acetaminophen must appear as part of the established name of the drug, as defined in § 299.4 of this chapter. Combination products containing acetaminophen and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name ''acetaminophen'' and the name(s) of the other active ingredient(s) in the product on the PDP in accord with this paragraph. Only the name ''acetaminophen'' must appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(iii) *For products labeled for adults only. Warnings.* The labeling of the product states the following warnings under the heading ''Warnings'':

(A) ''Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if you take [bullet] more than [insert maximum number of daily dosage units] in 24 hours [bullet] with other drugs containing acetaminophen [bullet] 3 or more alcoholic drinks every day while using this product''. This ''Liver warning'' must be the first warning under the ''Warnings'' heading. For products that contain both acetaminophen and aspirin, this ''Liver warning'' must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B) and before the ''Stomach bleeding warning'' in paragraph (a)(2)(iii)(A) of this section.

(B) ''Do not use [heading in bold type] with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure.''

(C) ''Ask a doctor before use if you have [heading in bold type] liver disease''.

(iv) *For products labeled only for children under 12 years of age*. (A) *Warnings*. The labeling of the product states the following warnings under the heading ''Warnings'':

(*1*) ''Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if the child takes [bullet] more than 5 doses in 24 hours [bullet] with other drugs containing acetaminophen''. This ''Liver warning'' must be the first warning under the ''Warnings'' heading.

(*2*) ''Do not use [heading in bold type] with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure.''

(*3*) ''Ask a doctor before use if the child has [heading in bold type] liver disease''.

(B) *Directions*. The labeling of the product contains the following information under the heading ''Directions'': ''this product does not contain directions or warnings for adult use'' [in bold type].

(v) *For products labeled for adults and children under 12 years of age*. *Warnings*. The labeling of the product states all of the warnings in paragraphs (a)(1)(iii)(A), (a)(1)(iii)(B), and (a)(1)(iii)(C) of this section with the following modifications:

(A) The Liver warning states ''Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if [bullet] adult takes more than [insert maximum number of daily dosage units] in 24 hours [bullet] child takes more than 5 doses in 24 hours [bullet] taken with other drugs containing acetaminophen [bullet] adult has 3 or more alcoholic drinks everyday while using this product.''

(B) ''Ask a doctor before use if the user [heading in bold type] has liver disease.''

(2) *Nonsteroidal anti-inflammatory analgesic/antipyretic active ingredients—including, but not limited to, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.*

(i) *Principal display panel*. The presence of an ''NSAID'' ingredient in the product must be prominently stated on the principal display panel (PDP), as defined in § 201.60.

(ii) *Statement of identity*. The statement of identity appears in accord with §§ 201.61, 299.4, and 343.50(a) of this chapter. The name of the NSAID ingredient and the word ''(NSAID)'' must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater: At least one-quarter as large as the size of the most prominent printed matter on the PDP, or at least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2). The word ''(NSAID)'' must appear as part of the established name of the drug, as defined in § 299.4 of this chapter, or after the general pharmacological (principal intended) action of the NSAID ingredient. For example, either of the following would be acceptable: Ibuprofen Tablets (NSAID) or Pain reliever/ fever reducer (NSAID). Combination products containing an NSAID and a nonanalgesic ingredient(s) (e.g., cough-cold) must include the name of the NSAID ingredient and the word ''(NSAID)'' in accord with this paragraph, and the name(s) of the other active ingredient(s) in the product on the PDP. Only the name of

the NSAID ingredient and the word ''(NSAID)'' need to appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(iii) *For products labeled for adults only. Warnings.* The labeling of the product states the following warnings under the heading ''Warnings'':

(A) ''Stomach bleeding warning [heading in bold type]: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you [bullet] are age 60 or older [bullet] have had stomach ulcers or bleeding problems [bullet] take a blood thinning (anticoagulant) or steroid drug [bullet] take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others] [bullet] have 3 or more alcoholic drinks every day while using this product [bullet] take more or for a longer time than directed''. This ''Stomach bleeding warning'' must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in § 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B). For products that contain both acetaminophen and aspirin, the acetaminophen ''Liver warning'' in § 201.325(a)(1)(iii) must appear before the ''Stomach bleeding warning'' in this paragraph.

(B) ''Ask a doctor before use if you have [heading in bold type] [bullet] stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain [bullet] ulcers [bullet] bleeding problems [bullet] high blood pressure [bullet] heart or kidney disease [bullet] taken a diuretic [bullet] reached age 60 or older''.

(C) ''Ask a doctor or pharmacist before use if you are [heading in bold type] [bullet] taking any other drug containing an NSAID (prescription or nonprescription) [bullet] taking a blood thinning (anticoagulant) or steroid drug''.

(D) ''Stop use and ask a doctor if [heading in bold type] [bullet] you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. [bullet] stomach pain or upset gets worse or lasts''.

(iv) *For products labeled only for children under 12 years of age. Warnings.* (A) The labeling of the product states the following warnings under the heading ''Warnings'':

(*1*) ''Stomach bleeding warning [heading in bold type]: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if the child [bullet] has had stomach ulcers or bleeding problems [bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing an NSAID (aspirin, ibuprofen, naproxen, or others) [bullet] takes more or for a longer time than directed''. The ''Stomach bleeding warning'' must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in §§ 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B).

(*2*) ''Ask a doctor before use if the child has [heading in bold type] [bullet] stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain [bullet] ulcers [bullet] bleeding problems [bullet] not been drinking fluids [bullet] lost a lot of fluid due to vomiting or diarrhea [bullet] high blood pressure [bullet] heart or kidney disease [bullet] taken a diuretic''.

(*3*) ''Ask a doctor or pharmacist before use if the child is [heading in bold type] [bullet] taking any other drug containing an NSAID (prescription or nonprescription) [bullet] taking a blood thinning (anticoagulant) or steroid drug''.

(*4*) ''Stop use and ask a doctor if [heading in bold type] [bullet] the child feels faint, vomits blood, or has bloody or black stools. These are signs of stomach bleeding. [bullet] stomach pain or upset gets worse or lasts''.

(B) *Directions*. The labeling of the product contains the following information under the heading ''Directions'': ''this product does not contain directions or warnings for adult use'' [in bold type].

(v) *For products labeled for adults and children under 12 years of age. Warnings*. The labeling of the product states all of the warnings in paragraphs (2)(iii)(A) through (2)(iii)(D) of this section with the following modifications:

(A) The Stomach bleeding warning states ''Stomach bleeding warning [heading in bold type]: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if the user [bullet] has had stomach ulcers or bleeding problems [bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others] [bullet] takes more or for a longer time than directed [bullet] is age 60 or older [bullet] has 3 or more alcoholic drinks everyday while using this product''. The ''Stomach bleeding warning'' must appear after the ''Reye's syndrome'' and ''Allergy alert'' warnings in §§ 201.66(c)(5)(ii)(A) and (c)(5)(ii)(B).

(B) The labeling states ''Ask a doctor before use if the user has [heading in bold type] [bullet] stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain [bullet] ulcers [bullet] bleeding problems [bullet] high blood pressure [bullet] heart or kidney disease [bullet] taken a diuretic [bullet] not been drinking fluids [bullet] lost a lot of fluid due to vomiting or diarrhea [bullet] reached age 60 or older.''

(C) The labeling states ''Ask a doctor or pharmacist before use if the user is [heading in bold type] [bullet] taking any other drug containing an NSAID (prescription or nonprescription) [bullet] taking a blood thinning (anticoagulant) or steroid drug''.

(D) The labeling states ''Stop use and ask a doctor if [heading in bold type] [bullet] the user feels faint, vomits blood, or has bloody or black stools. These are signs of stomach bleeding. [bullet] stomach pain or upset gets worse or lasts''.

(vi) *Active ingredient(s)*. The active ingredient(s) section of the product's labeling, as defined in § 201.66(c)(2), contains the term ''(NSAID)*'' after the NSAID active ingredient with an asterisk statement at the end of the active ingredient(s) section that defines the term ''NSAID'' and states ''* nonsteroidal anti-inflammatory drug.''

(b) *New warnings information statement*. The labeling of any drug product subject to this section that is initially introduced or initially delivered for introduction into interstate commerce before the effective date and within 12 months after the effective date of the final rule or if relabeled at any time before the effective date of the final rule must bear on its principal display panel (PDP), as defined in § 201.60, the statement ''See new warnings information.'' This statement must appear highlighted (e.g., fluorescent or color contrast) or in bold type, be in lines generally parallel to the base on which the package rests as it is designed to be displayed, and be in one of the following sizes, whichever is greater:

(1) At least one-quarter as large as the size of the most prominent printed matter on the PDP, or

(2) At least as large as the size of the ''Drug Facts'' title, as required in § 201.66(d)(2).

(c) *Requirements to supplement approved application*. Holders of approved applications for OTC drug products that contain internal analgesic/antipyretic active ingredients that are subject to the requirements of paragraph

(a) of this section must submit supplements under § 314.70(c) of this chapter to include the required information in the product's labeling. Such labeling may be put into use without advance approval of FDA provided it includes at least the exact information included in paragraph (a) of this section.

(d) *Regulatory action.* Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after [date 12 months after date of publication of the final rule in the **Federal Register**] is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and is subject to regulatory action. Any drug product for which the labeling required in this section was voluntarily implemented before the date of publication of the final rule that is initially introduced or initially delivered for introduction into interstate commerce after [date 18 months after date of publication of the final rule in the **Federal Register**] and that is not labeled as required is misbranded under section 502 of the act and is subject to regulatory action.

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

4. The authority citation for 21 CFR part 343 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

5. Section 343.50, as proposed at 53 FR 46255, November 16, 1988, and 67 FR 54158, August 21, 2002, is further amended by revising paragraphs (c)(1)(i), (c)(1)(iii), (c)(1)(iv)(A), (c)(1)(v)(A) through (c)(1)(v)(C), (c)(1)(ix)(A), (c)(1)(ix)(B), (c)(1)(ix)(C), (c)(1)(ix)(E), (c)(2)(i), (c)(2)(iii), (c)(2)(iv)(A),

(c)(2)(v)(A) through (c)(2)(v)(C)[3] and adding new paragraphs (b)(4)(i)(C) and (c)(3)(i) through (c)(3)(v)(C) to read as follows:

§ 343.50 Labeling of analgesic-antipyretic drug products.

* * * * *

(b) * * *

(4) * * *

(i) * * *

(C) The product states the following statement under the heading ''Directions,'' ''this product does not contain directions or warnings for adult use''. This statement is not required for products containing ibuprofen as identified in § 343.10 (g).

* * * * *

(c) * * *

(1) * * *

(i) For products containing any ingredient in § 343.10 (a) through (f) The labeling states ''Stop use and ask a doctor if [heading in bold type] [bullet][1] pain gets worse or lasts more than 10 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] any new symptoms appear''.

* * * * *

(iii) *For products containing acetaminophen identified in § 343.10(a)*. The labeling states the warnings in § 201.325(a)(1)(iii)(A), (a)(1)(iii)(B), and (a)(1)(iii)(C) and the following statement must follow the general warning identified in § 330.1(g) of this chapter: ''Prompt medical attention is critical

[3]The warnings in these sections are revised to conform with § 201.66 (Drug Facts format). Other warnings remain as proposed in the TFM and will be revised into the Drug Facts format in a future issue of the **Federal Register**.

[1]See § 201.66(b)(4) of this chapter for definition of bullet symbol.

for adults as well as for children even if you do not notice any signs or symptoms.''

(iv) * * *

(A) The labeling states the warning in paragraph (c)(1)(v)(B) plus the bulleted statement ''asthma''.

* * * * *

(v) * * *

(A) The labeling states the warning in paragraph (c)(1)(i) of this section plus ''[bullet] you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. [bullet] stomach pain or upset gets worse or lasts [bullet] ringing in the ears or loss of hearing occurs''.

(B) The labeling states ''Ask a doctor before use if you have [heading in bold type] [bullet] stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain [bullet] ulcers [bullet] bleeding problems [bullet] high blood pressure [bullet] heart or kidney disease [bullet] taken a diuretic [bullet] reached age 60 or older''.

(C) The labeling states ''Ask a doctor or pharmacist before use if you are [heading in bold type] [bullet] taking any other drug containing an NSAID (prescription or nonprescription) [bullet] taking a blood thinning (anticoagulant) or steroid drug [bullet] taking a prescription drug for diabetes, gout, or arthritis''.

* * * * *

(ix) * * *

(A) The stomach bleeding warning set forth in § 201.325(a)(2)(iii)(A), (a)(2)(iv)(A), or (a)(2)(v)(A) of this chapter appears after the subheading ''Stomach bleeding warning:''.

(B) The labeling states ‘‘Ask a doctor before use if you have [heading in bold type] [bullet] problems or serious side effects from taking pain relievers or fever reducers [bullet] stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain [bullet] ulcers [bullet] bleeding problems [bullet] high blood pressure [bullet] heart or kidney disease [bullet] taken a diuretic [bullet] reached age 60 or older’’.

(C) The labeling states ‘‘Ask a doctor or pharmacist before use if you are [heading in bold type] [bullet] taking any other drug containing an NSAID (prescription or nonprescription [bullet] taking a blood thinning (anticoagulant) or steroid drug [bullet] under a doctor’s care for any serious condition [bullet] taking any other drug’’.

* * * * *

(E) In addition to the warning required in § 201.324(c) of this chapter after the subheading ‘‘Stop use and ask a doctor if’’ [heading in bold type], the following statements also appear: ‘‘[bullet] you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding. [bullet] pain gets worse or lasts more than 10 days [bullet] fever gets worse or lasts more than 3 days [bullet] stomach pain or upset gets worse or lasts [bullet] redness or swelling is present in the painful area [bullet] any new symptoms appear‘‘.

* * * * *

(2) * * *

(i) For products containing any ingredient in § 343.10 (a) through (f) The labeling states ‘‘Stop use and ask a doctor if [heading in bold type] [bullet] pain gets worse or lasts more than 5 days [bullet] fever gets worse or lasts

more than 3 days [bullet] redness or swelling is present [bullet] any new symptoms appear ''.

* * * * *

(iii) *For products containing acetaminophen identified in § 343.10(a).* The labeling states the warnings in § 201.325(a)(1)(iv)(A)(1), (a)(1)(iv)(A)(2), and (a)(1)(iv)(A)(3) and the following statement must follow the general warning identified in § 330.1(g) of this chapter: ''Prompt medical attention is critical even if you do not notice any signs or symptoms.''

(iv) * * *

(A) The labeling states the warning in paragraph (c)(2)(v)(B) plus the bulleted statement ''asthma''.

* * * * *

(v) * * *

(A) The labeling states the warning in paragraph (c)(2)(i) of this section plus ''[bullet] the child feels faint, vomits blood, or has bloody or black stools. These are signs of stomach bleeding. [bullet] stomach pain or upset gets worse or lasts [bullet] ringing in the ears or loss of hearing occurs''.

(B) The labeling states ''Ask a doctor before use if the child has [heading in bold type] [bullet] stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain [bullet] ulcers [bullet] bleeding problems [bullet] not been drinking fluids [bullet] lost a lot of fluid due to vomiting or diarrhea [bullet] high blood pressure [bullet] heart or kidney disease [bullet] taken a diuretic''.

(C) The labeling states ''Ask a doctor or pharmacist before use if the child is [heading in bold type] [bullet] taking any other drug containing an NSAID (prescription or nonprescription) [bullet] taking a blood thinning

(anticoagulant) or steroid drug [bullet] taking a prescription drug for diabetes, gout, or arthritis''.

* * * * *

(3) * * *

(i) For products containing any ingredient in § 343.10 (a) through (f). The labeling states ''Stop use and ask a doctor if [heading in bold type] [bullet] adult's pain gets worse or lasts more than 10 days [bullet] child's pain gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] any new symptoms appear''.

(ii) The warning in § 343.50(c)(1)(ii), if applicable.

(iii) *For products containing acetaminophen identified in § 343.10(a).* The labeling states the warnings in § 201.325(a)(1)(v) of this chapter. The warning in § 201.325 (a)(1)(v)(B) is modified to read: '' Ask a doctor before use if the user [heading in bold type] [bullet] has liver disease [bullet] is a child with pain of arthritis''. The following statement must follow the general warning identified in § 330.1(g) of this chapter: ''Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.''

(iv) The warnings in § 343.50(c)(1)(iv), if applicable.

(*v*) *For products containing aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate identified in §§ 343.10(b), (c), (d), (e) and (f).*

(A) The labeling states the warning in paragraph (c)(3)(i) of this section plus ''[bullet] the user feels faint, vomits blood, or has bloody or black stools.

These are signs of stomach bleeding. [bullet] stomach pain or upset gets worse or lasts [bullet] ringing in the ears or loss of hearing occurs''.

(B) The labeling states the warning in § 201.325(a)(2)(v)(B) plus ''[bullet] is a child with pain of arthritis''.

(C) The labeling states the warning in § 201.325(a)(2)(v)(C) plus ''[bullet] taking a prescription drug for diabetes, gout, or arthritis''.

Dated: November 22, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 06–????? Filed ??–??–06; 8:45 am]

BILLING CODE 4160–01–S