DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. FDA-1977-N-0013] (formerly Docket No. 1977N-0094L)

RIN 0910-AF36

Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing this final rule to require important new organ-specific warnings and related labeling for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic (IAAA) drug products. The new labeling informs consumers about the risk of liver injury when using acetaminophen and the risk of stomach bleeding when using nonsteroidal anti-inflammatory drugs (NSAIDS). The new labeling is required for all OTC IAAA drug products whether marketed under an OTC drug monograph or an approved new drug application (NDA).

DATES: Effective Date: This final rule is effective [insert date 12 months after date of publication in the FEDERAL REGISTER].

Compliance Date: The compliance date for all products subject to this final rule, including products with annual sales less than $25,000, is [insert date 12 months after date of publication in the FEDERAL REGISTER].

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SUPPLEMENTARY INFORMATION:

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Glossary

(The definitions of terms used throughout this document are included in this glossary because these terms are likely to be unfamiliar to many readers.)

AERS: FDA's Adverse Event Reporting System; a database of adverse events reported to FDA for drugs and medical devices

Acute Liver Failure: Severe liver injury without a history of chronic liver disease that is associated with coagulopathy and encephalopathy

ALT: Alanine aminotransferase; a liver enzyme that is often tested to evaluate individuals for liver disease

AST: Aspartate aminotransferase; a liver enzyme that is often tested to evaluate individuals for liver disease

CFR: The Code of Federal Regulations; list of regulations created by the executive departments and agencies of the Federal Government

GRAS/E: Generally recognized as safe and effective

GSH: Glutathione; tripeptide (protein fragment) necessary for acetaminophen metabolism to avoid accumulation of the toxic metabolite N-acetyl-p-benzo-quinone imine (NAPQI)

HIV: Human immunodeficiency virus; a retrovirus that can lead to acquired immunodeficiency syndrome (AIDS)

IAAA: Internal analgesic, antipyretic, and antirheumatic drug products

INR: International normalized ratio; measurement that evaluates the ability of blood to clot

IU/L: International units per liter

NAQPI: N-acetyl-p-benzo-quinone imine; a harmful by-product of acetaminophen metabolism that can cause severe liver injury

NDA: New Drug Application; application needed for approval of a new drug by the FDA prior U.S. marketing

NSAIDs: Nonsteroidal anti-inflammatory drugs (such as aspirin and ibuprofen)

PDP: Principal display panel; part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.

I. Overview of This Document

This document addresses comments and data in the 19 submissions that we received in response to the December 26, 2006 (proposed rule) (71 FR 77314), which is described in section II of this document. The submissions comment on the labeling that we proposed for 21 CFR parts 201 and 343 as well as other issues where specific comments were sought in the 2006 proposed rule. The proposed rule asked for comments on issues related to the following:

- The safe and effective daily dose of acetaminophen
- Daily dose recommendation for alcohol abusers
- Combination products of acetaminophen combined with methionine or acetylcysteine
- Package size and configuration limitations with acetaminophen products
- Label warnings for individuals with Human Immunodeficiency Virus (HIV)
- Drug interactions between acetaminophen and warfarin

This document states our final conclusions on the labeling requirements in 21 CFR part 201 and requires that manufacturers include this labeling on their OTC IAAA drug products by the effective date identified in this document (see DATES). We are currently

evaluating data and information regarding the remaining issues discussed in the proposed rule, some of which include the following:

- Safe daily dose for acetaminophen (healthy users)
- Safe daily dose for acetaminophen users with chronic liver disease
- Safe daily dose for acetaminophen with alcohol use
- Appropriate dosage for acetaminophen efficacy
- Package size restrictions for OTC IAAA drug products
- Pediatric dosing for OTC IAAA drug products
- Various warnings for OTC IAAA drug products that were proposed in 21 CFR part 343 but not part 21 CFR part 201
- Acetaminophen-narcotic combinations
- Combinations of acetaminophen and N-acetylcysteine (NAC) or methionine
- Prescription labeling for OTC IAAA drug products
- Education on safe use of OTC IAAA drug products

We believe these are very important issues and will address them in separate FEDERAL REGISTER notices that address the OTC IAAA drug monograph (21 CFR part 343). We are not addressing them in this document because we believe there is a major public health benefit to having the labeling in 21 CFR part 201 appear on products as soon as possible. This new labeling in 21 CFR part 201 will advise consumers about serious risks associated with using these products. By not addressing other issues in this document that we are still evaluating, we are able to more quickly implement the labeling in 21 CFR part 201.

In this document, we are requiring the labeling changes proposed in the 2006 proposed rule (see Table 1). In response to the submissions, we are also requiring the following labeling

that was not specifically proposed in the 2006 proposed rule but was suggested by the submissions received:

● Liver warning and stomach bleeding warnings required on immediate container labels in addition to the carton or outer container for all OTC IAAA drug products (21 CFR 201.326(a)(1)(iii)(A) and 21 CFR 201.326(a)(2)(iii))

● Revised acetaminophen concomitant use warning (21 CFR 201.326(a)(1)(iii)(B))

● New warning about taking warfarin and acetaminophen at the same time (21 CFR 201.326(a)(1)(iii)(D))

● Revised directions statement for all OTC IAAA drug products labeling for children under 12 years of age (21 CFR 201.326(a)(1)(iv)(B))

● Revised introductory sentence for stomach bleeding warning (21 CFR 201.326(a)(2)).

In addition, we are allowing voluntary highlighting of information under the "Active Ingredient" and "Purpose" headings in Drug Facts for all OTC IAAA drug products.

It should be noted that the 2006 proposed rule discussed added labeling requirements in 21 CFR 201.325. However, in December 2007, we added required labeling for OTC vaginal contraceptives in 21 CFR 201.325 (72 FR 71769). Therefore, in this document, required labeling for OTC IAAA drug products is be added to 21 CFR 201.326.

II. Rulemaking History for OTC IAAA Drug Products

The rulemaking history in this document focuses on rulemakings that discuss labeling related to liver injury caused by acetaminophen and/or related to stomach bleeding caused by NSAIDs.

A. Rulemakings Published Before the 2006 Proposed Rule

In 1977, we published the report from the Advisory Review Panel on OTC IAAA Drug

Products (the Panel) (42 FR 35346). In its report, the Panel recommended the following warnings related to stomach bleeding and liver injury, respectively:

- For products containing 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 35493)

- For products containing acetaminophen:

  Do not exceed the recommended dosage because severe liver damage may occur (42 FR 35346 at 35494)

Based on the Panel's report, we published a 1988 proposed rule, referred to as a tentative final monograph (53 FR 46204). In the 1988 proposed rule, we tentatively adopted the Panel's recommended aspirin warning with a slight modification. We decided not to adopt the liver warning for acetaminophen as recommended by the Panel because we concluded that warnings need not include information on the specific injury to organs of the body caused by an acute overdose of a drug (53 FR 46204 at 46214). However, we proposed a modified warning because we believed consumers should know that prompt medical attention is essential if an acetaminophen overdose occurs (53 FR 46204 at 46215). In the proposed rule, we included the following warnings related to stomach bleeding and liver injury, respectively (53 FR 46204 at 46256):

- For products containing 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 (proposed 21 CFR 343 (c)(1)(v)(B)).

- For products containing acetaminophen:

  Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms (proposed 21 CFR 343.50 (c)(1)(iii)).

This warning for products containing acetaminophen includes the general overdose warnings in 330.1(g), as required in proposed 21 CFR 343.50 (c)(1)(iii).

In 1998, we published two final rules that (1) provide labeling information to health professionals (i.e., labeling that is not available on OTC IAAA drug products) that includes cardiovascular and rheumatologic indications for aspirin (63 FR 56802), and (2) require an alcohol warning for all IAAA drug products in 21 CFR 201.322 (63 FR 56789) as follows:

- For products containing acetaminophen:

  Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask a doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

- For products containing NSAIDs:

  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.

In 2002, we issued a proposed rule to include ibuprofen as a GRASE active ingredient in the monograph for OTC IAAA drug products (67 FR 54139). The proposed rule includes additional warnings relating to stomach problems, ulcers, bleeding problems, high blood pressure, heart or kidney disease, and use of diuretics. The warnings also include information specific to consumers over 65 years of age.

B. 2006 Proposed Rule

On December 26, 2006, we published a proposed rule regarding IAAA drug products (71 FR 77314). In the proposed rule, we proposed new organ-specific warnings and related labeling for all OTC IAAA drug products. The proposed labeling was designed to provide consumers with information concerning liver injury caused by acetaminophen and stomach bleeding caused by NSAIDs. We stated in the proposed rule that, when labeled appropriately and used as directed, OTC IAAA drug products are safe and effective drug products that benefit tens of millions of consumers every year and that these products should continue to be available to consumers in the OTC setting (71 FR 77314 at 77315). However, we also stated that new labeling is necessary to ensure consumers know these products can cause liver injury and stomach bleeding (71 FR 77314 at 77331).

1. Scientific Basis for 2006 Proposed Rule

As explained in the proposed rule, after reviewing a variety of data demonstrating a risk for these two adverse drug effects, we are concerned about liver injury and stomach bleeding associated with IAAA drug products. For acetaminophen, we analyzed data from national databases including emergency departments, hospital discharges, mortality data, poison control centers, and spontaneous post-marketing drug adverse event reports reported to us through our

AERS database from 1990-2001. In addition, we considered results of acute liver failure studies in the United States that were published by the U.S. Acute Liver Failure Study Group as well as case series from the University of Pennsylvania Hospital. We concluded from this data that unintentional overuse of acetaminophen is associated with a large number of emergency department and hospital admissions and is related to an estimated 100 deaths each year. For NSAIDs, we primarily considered post-marketing case reports of stomach bleeding and kidney injury collected by AERS between 1998 and 2001. We concluded from this data that serious stomach bleeding events can occur when NSAIDs are used according to the warnings and directions on the OTC label.

2. 2006 Proposed Rule Labeling

The proposed labeling was supported by our interpretation of the data and was consistent with recommendations that we received from an FDA Advisory Committee that met in 2002 to discuss OTC IAAA drug products. The committee unanimously agreed that the evidence of risk associated with unintentional overuse warrants a liver injury warning for OTC drug products containing acetaminophen (71 FR 77314 at 77323 to 77324) and that for OTC NSAIDs data support a stomach bleeding warning (71 FR 77314 at 77327). The committee recommended that the terms "acetaminophen" (71 FR 77314 at 77323) and "NSAIDs" (71 FR 77314 at 77328) appear prominently on the front panel or principal display panel (PDP) of product labeling (so consumers are aware that acetaminophen or NSAIDs are present in the products they are using to prevent unintentional overdose). The committee also recommended an alcohol warning separate from the liver injury and stomach bleeding warnings, but we choose to combine the warnings (71 FR 77314 at 77331). We discuss this decision further in section IV.A.5. of this document. The 2006 proposed rule also included additional warnings for these products (see Table 1).

TABLE 1. OVERVIEW OF PROPOSED LABELING CHANGES FOR OTC IAAA DRUG PRODUCTS IN 2006 PROPOSED RULE

Type of Product	Proposed Labeling Requirements
Acetaminophen products	● Warning to include information on severe liver injury ● Ingredient name (i.e., "Acetaminophen") highlighted or in bold type and in a prominent print size on the PDP ● Statement "See new warnings information" highlighted or in bold type and in a prominent print size on the PDP for 12 months following publication of this rule ● Alcohol warning as part of liver warning (instead of separate alcohol warning previously required in 21 CFR 201.322)
NSAID products	● Warning to include information on severe stomach bleeding ● Ingredient name (e.g., "Aspirin") highlighted or in bold type on the PDP ● Term "(NSAID)" highlighted or in bold type and in a prominent print size on the PDP as part of the established name of the drug or after the general pharmacological (principal intended) action of the NSAID ingredient ● Statement "See new warnings information" highlighted or in bold type and in a prominent print size on the PDP for 12 months following publication of this rule ● Alcohol warning as part of stomach bleeding warning (instead of separate alcohol warning previously required in 21 CFR 201.322)
Combination products containing acetaminophen or an NSAID plus a non-analgesic ingredient	● All ingredient names (e.g., "Acetaminophen" or "Aspirin") highlighted or in bold type and in a prominent print size and the names of the other active ingredients on the PDP ● Term "(NSAID)" highlighted or in bold type and in a prominent print size on the PDP as part of the established name of the drug or after the general pharmacological (principal intended) action of the NSAID ingredient if the product contains an NSAID ingredient

III. Discussion of Submissions Regarding Proposed Labeling for All OTC Internal Analgesics

A. PDP

1. General Issues

Some of the submissions concern labeling that appears on the PDP of all OTC IAAA

drug products (i.e., acetaminophen and NSAIDs). A manufacturer of OTC acetaminophen products (Ref. 1) agrees that the proposed PDP labeling is beneficial to consumers. The manufacturer states that, prior to the 2006 proposed rule, it had voluntarily implemented labeling similar to the proposed labeling. Another submission (Ref. 2) argues that the proposed labeling may cause crowding on the PDP, making it difficult for consumers to read the label. The submission contends that to accommodate the proposed labeling, manufacturers may be forced to increase the size of their packages, which could have significant economic consequences for industry. A third submission (Ref. 3) questions the readability of the warnings on OTC NSAID products, arguing that the print size is too small. The submission suggests placing the warnings on the PDP in bold print to increase the readability of important warnings.

We are not revising the proposed PDP labeling in this document. We believe the proposed labeling, including highlighting the terms acetaminophen or NSAIDs on the PDP, is important to help ensure the safe and effective use of OTC IAAA drug products. We disagree that the required labeling will cause crowding on the PDP. If a PDP is crowded, manufacturers can reduce the font size of the trade name and promotional material to allow room for the labeling required in this document. Reducing the prominence of the trade name and promotional material will not decrease the safety or efficacy of OTC IAAA drug products. It is important that consumers be able to identify products that contain acetaminophen and NSAIDS. We believe that manufacturers should be able to include the name of the ingredient on the PDP as specified in the proposed rule without having to increase the package sizes. Because all manufacturers will be equally affected by these requirements, there is no marketing disadvantage to certain manufacturers, as argued by some submissions.

We disagree that the print size of the warnings on OTC IAAA drug products is too small

and that the warnings should appear on the PDP in bold print. OTC drug regulations (21 CFR 201.66(d)(2)) require that warnings on all OTC drug products appear in a standard Drug Facts format and specify minimum type sizes. We developed these regulations based, in part, on data concerning readability of different font sizes.

We believe the statement "see new warnings" that is required on the PDP (21 CFR 201.326(b)) and that refers consumers to the warnings in Drug Facts is adequate without including the actual warnings on the PDP. Including the warnings themselves would require a large amount of the available PDP space and would make the information on the PDP difficult to read because of crowding or could require larger package sizes.

2. Statement of Identity

Three submissions address the statement of identity required on the PDP. The first submission (Ref. 4) supports the proposed prominence of the statement of identity. The second submission (Ref. 2) proposes revising the statement of identity on OTC acetaminophen products from "acetaminophen" to "contains acetaminophen." Likewise, the second submission proposes revising the statement of identity on OTC NSAID products from "(name of the NSAID), NSAID" to "contains (name of NSAID), a pain medication." The second submission argues that consumers may be confused without this revision because the term "acetaminophen" identifies an active ingredient while the term "NSAID" describes a class of drugs.

The third submission (Ref. 5) argues that requiring the statement of identity in a type size at least one-quarter as large as the most prominent print is unnecessary and arbitrary. The submission contends that we do not have data to support this requirement. The submission suggests that the statement of identity should be as large as the "Drug Facts" title on the outside container, giving it adequate prominence without crowding the PDP or inhibiting brand

competition. The submission argues that consumers should primarily refer to the Drug Facts box, rather than the PDP, for information concerning the safe and effective use of OTC drug products. The submission also requests that we require only the term "NSAID" to be highlighted on the PDP, rather than highlighting both "NSAID" and the active ingredient as proposed. The submission argues that this change would be consistent with a June 2005 letter that we sent to NDA holders for OTC NSAID products (Ref. 6).

We disagree with the two submissions arguing that the statement of identity requirements in the 2006 proposed rule should be revised. We do not believe it is necessary to require the statement of identity on the PDP to include "contains" before the active ingredient, as argued by one of the two submissions. The statement of identity without "contains" is consistent with the statement of identity required on all OTC drug products (21 CFR 201.61). We believe the name of the active ingredient followed by the pharmacological category is clear without adding the word "contains." For example, the statement of identity for an OTC ibuprofen product– "ibuprofen (NSAID), pain reliever/fever reducer"– allows consumers to recognize the active ingredient and pharmacological action of the active ingredient. For this same reason, we do not believe addition of "pain medication" is necessary in the NSAID statement of identity.

The other submission discusses statement of identity requirements that are general requirements for all OTC drug products and are not specific to OTC IAAA products. We do not believe it is appropriate to address these requirements for all OTC drug products in this document, which is specific to OTC internal analgesics. If any parties would like us to revise the statement of identity requirements because of crowding or other concerns, we suggest they submit a citizen petition in accordance with 21 CFR 10.30. Such a petition could address the requirements for all OTC drug products.

We agree with the submission requesting that we require only the term "NSAID" to be highlighted on the PDP, rather than both the ingredient name and "NSAID." This would be consistent with the June 2005 letter that we sent to NDA holders and would avoid the need for manufacturers to re-label products that otherwise comply with this rule. The purpose of highlighting "NSAID" is to prevent consumers from using multiple NSAID products at the same time. Highlighting only "NSAID" should achieve this intent. Therefore, we are revising the NSAID statement of identity in this document (21 CFR 201.326(a)(2)(i)) to require only highlighting of "NSAID."

3. Warning Flag

We received a submission (Ref. 5) concerning the proposed warning flag: "See new warnings information" (proposed 21 CFR 201.325(vi)(b)). The submission argues that the proposed type size (i.e., one-quarter as large as the most prominent print) is unnecessary and arbitrary. The submission contends that we have no data to support this requirement. The submission also suggests that we should not require the warning flag in type parallel to the package base because it is unnecessarily restrictive, arguing that 45 degrees is just as effective. The submission requests that we only require the warning flag for 6 or 9 months after the final rule publishes rather than for one year, as proposed. Alternatively, the submission requests that we allow exemptions after publication of the final rule if a product has already contained a "new" flag (i.e., a flag that states "new" and refers to a new formulation, new flavor, etc.). Finally, the submission suggests that we allow flexibility so that a product does not have to concurrently include a "new" flag and the proposed warning flag.

We disagree with the submission. We continue to believe that requiring the flag to be displayed in a standard format, parallel to the drug product package base and in a minimum size

(at least one-quarter as large as the most prominent type size) on the PDP will make this information more easily seen by consumers. We do not believe the size is unnecessary and arbitrary. We believe the flag must be prominent and proposed the minimum size to be one of the following, whichever is larger:

- At least one-quarter as large as the most prominent type size or
- At least as large as the size of the "Drug Facts" title (21 CFR 201.326(b)).

We believe this proposal ensures that consumers will see the flag while allowing manufacturers labeling flexibility. Furthermore, we believe that it is more important to make consumers aware of new warning information than it is of other promotional material such as "new" taste.

We are not revising the labeling requirements in the 2006 proposed rule to accommodate other "new" flags that manufacturers choose to place on the PDP (i.e., a flag that states "new" and refers to a new formulation, new flavor, etc.). These "new" flags are generally promotional in nature and are not related to the safe and effective use of OTC IAAA drug products. Therefore, manufacturers need to determine whether and how to display any promotional material on their products without interfering with the "See New Warnings" flag. We will require that the "See New Warnings" flag appear on the PDP for one year after the final rule is published, rather than for the 6 or 9 months suggested by the submission. Because of the nature of the new warnings, we continue to believe that educating consumers about the risks associated with OTC IAAA drug products is very important and more likely to be successful if the flag remains on products for 1 year.

B. Drug Facts

We received four submissions concerning the proposed Drug Facts labeling. The first submission (Ref. 5) seeks clarification about whether we will allow voluntary highlighting of the

active ingredient and purpose (i.e., "pain reliever/fever reducer") section in Drug Facts to draw attention to the presence of acetaminophen. The submission points out that many marketed OTC internal analgesic products are already labeled as such. The second and third submissions concern the "Warnings" section of Drug Facts. The second submission (Ref. 7) opposes additional warnings on OTC internal analgesics for the following reasons:

● Because these medicines have been used for a long time, consumers will not change their usage patterns even if additional warnings appear in the labeling.

● The proposed warnings would reduce the impact of similar warnings on other dangerous drugs.

The submission proposes to inform the public about new safety concerns through press releases rather than by requiring more warnings on the label. The third submission (Ref. 2) is concerned that the proposed warnings may cause consumers to avoid OTC internal analgesic products because of the emphasis on risks.

The first and fourth submissions concern the "Directions" section of Drug Facts. Both submissions agree with the proposed required statement in "Directions" on products labeled only for use by children: "This product does not contain directions or warnings for adult use." The fourth submission (Ref. 1) requests that we allow flexibility to place this statement under the "Do not use" subheading of the "Warnings" section instead of in the "Directions" section. The argument is that the "Directions" section of pediatric OTC drug products is often lengthy and crowded with information. The first submission (Ref. 5) points out that we asked companies to submit supplements with the phrase "directions or complete warnings" in the July 2005 letter to NDA holders of OTC NSAID products (Ref. 6). The submission requests that we allow the use of the word "complete" so that OTC NSAID products that otherwise comply with this rule do not

have to be relabeled.

We agree with the first submission and are revising the statement in the "Directions" section of pediatric internal analgesic products to read, "This product does not contain directions or complete warnings for adult use." We believe consumers will better understand the meaning of this revised statement compared to the proposed statement. This revision also makes the statement consistent with the June 2005 letter to holders of NDAs for NSAID products. This revision prevents products that already include this statement and otherwise comply with this rule from having to be relabeled. Similarly, we will allow voluntary highlighting of the "active ingredient and its purpose" section in Drug Facts to increase the prominence of the active ingredient and to be consistent with the labeling of many currently marketed OTC IAAA drug products, avoiding the need for re-labeling of products that otherwise comply with this rule. We are allowing this voluntary highlighting because of the seriousness of liver injury that may result from use of multiple acetaminophen-containing products at the same time.

We disagree with most of the comments in the second submission (Ref. 8). The submission does not include any information or data supporting its belief that the warnings in the 2006 proposed rule will not change consumer behavior when using OTC IAAA drug products. We do agree with this submission that press releases can help educate consumers about the potential risks associated with OTC IAAA drug products. However, product labeling is the most important means to ensure that consumers have access to important warning information each time the drug product is purchased and used. We disagree with the third submission that additional warnings may cause consumers to avoid using OTC IAAA drug products because of the emphasis on risks. We are not aware of data supporting the submission's argument. The warnings identify risks that we believe consumers need to know in order to use these products

safely.

We disagree with the fourth submission (Ref. 1) requesting that we allow flexibility to place the Directions statement under the "Do not use" subheading of the "Warnings" section. Although we agree that the "Directions" section of pediatric OTC drug products is often crowded with other information, we believe that because pediatric drug products are dispensed by adults, it is important that the placement of this statement be consistent with OTC IAAA drug products intended for adults.

C. Immediate Container

We received a submission (Ref. 9) that believes there is a "dire need" for the proposed labeling and suggests that, in addition to the outer container, we should also require the proposed labeling on the immediate container. We agree with the submission. Consumers may discard the carton or outer container, which contains the Drug Facts box, after purchasing an OTC drug product. Therefore, important warnings, directions, and other Drug Facts information may not be available to consumers every time they use a product. While we believe that OTC IAAA drug products can be safe and effective when used as directed, it is important to alert consumers that acetaminophen can potentially cause liver injury and NSAIDs can potentially cause stomach bleeding. Because of the serious consequences associated with these adverse events, we believe that the associated warnings should be available every time an OTC IAAA drug product is used. Therefore, we are requiring that the liver warning appear on the immediate container of all OTC internal analgesic drug products containing acetaminophen (21 CFR 201.326(a)(1)(iii)(A)). Likewise, we are requiring that the stomach bleeding warning appear on the immediate container of all OTC internal analgesic drug products containing an NSAID (21 CFR 201.326(a)(2)(iii)(A)).

If the immediate container of an OTC IAAA drug product is a blister pack, the labeling space may need to be expanded to accommodate these warnings along with other required labeling. We believe the need for these warnings justifies any expansion of labeling space that may be necessary. Ideally, the blister pack should be designed so that the warnings can be read after removal of individual doses from the blister pack.

IV. Labeling Required for OTC Acetaminophen

A. Liver Warning

In this document, we are requiring a liver warning that is identical to the warning in the 2006 proposed rule except the first bulleted statement is modified slightly. We proposed three similar versions of this warning in the 2006 proposed rule (71 FR 77314 at 77349 to 77350): (1) one for products labeled for adults only, (2) one for products labeled for children under 12 years of age only[1], and (3) one for products labeled for adults and children under 12 years of age[2]. The proposed warning for adults reads as follows:

> 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.

In the 2006 proposed rule, we explain that the liver warning is necessary to advise

[1]The wording of the warning for children under 12 years of age only reads: "Liver warning: 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."

[2]The wording of the warning for adults and children under 12 years of age reads: "Liver warning: 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] taken with other drugs containing acetaminophen [bullet] adult has 3 or more alcoholic drinks every day while using this product."

consumers about the occurrence of unintentional liver injury associated with ingesting too much acetaminophen (i.e., more than the maximum daily dose of 4 grams). In that document, we present data and evidence supporting the need for the liver warning. The proposed liver warning also includes a version of the alcohol warning already required for all OTC drug products labeled for adult use that contain acetaminophen or NSAIDs (21 CFR 201.322). We proposed incorporating the alcohol warning into the liver warning because the alcohol warning for acetaminophen relates to liver injury. In addition, we believe that one warning may be more likely to be read and understood by consumers.

We received many submissions expressing support for the proposed liver warning. Two of these submissions state that, although acetaminophen is generally a safe drug, it can cause severe and even fatal liver injury in certain cases, such as simultaneously using multiple drugs containing acetaminophen (Refs. 10 and 11). One of these submissions states that it is important for consumers to be aware that acetaminophen must be used in appropriate doses and in the right circumstances to avoid liver injury (Ref. 10). Another submission states that our liver warning is appropriate because the risk of liver injury with acetaminophen use is well documented (Ref. 12). The submission also argues that the proposed liver warning will provide information to consumers regarding the risk of liver injury and predisposing conditions as well as actions they may take to minimize the risk of liver injury. Only one submission argues that a liver warning is not needed (Ref. 1). The submission also argues that, if we do require the warning, we should modify the liver warning language. Another submission also recommends that we modify the wording of the proposed liver warning (Ref. 11).

All of the submissions related to the liver warning are discussed in the next five sections of this document. The first section (IV.A.1.) discusses scientific support for the liver warning.

The second section (IV.A.2.) discusses the introductory sentences of the warning. The third, fourth, and fifth sections (IV.A.3. through IV.A.5.) discuss the three bulleted statements of the liver warning, respectively.

1. Scientific Support for the Liver Warning

One submission states that it is inappropriate for us to rely on the case series and databases cited in the 2006 proposed rule to support the need for a liver warning (Ref. 1). The submission argues that these data sources have serious limitations, and those limitations prevent the data from demonstrating that therapeutic doses of acetaminophen (i.e., no more than 4 grams daily for not longer than 10 days) cause liver injury, according to the submission. The submission provides a reanalysis of the same databases and case series described in the 2006 proposed rule plus data from more recent years. The submission also includes the annual number of patients receiving liver transplants associated with drug-related acute liver failure from the United Network for Organ Sharing (UNOS) database. Based on these data, the submission argues that acetaminophen overdoses, acetaminophen-associated liver injury, and acetaminophen-associated deaths, whether intentional or unintentional, are not increasing. The submission also states that hospital rates for acute liver failure in the United States from 1999 through 2006 have been fairly stable.

Despite the information in this submission, we still believe that overuse of acetaminophen, whether intentional or unintentional, is associated with severe liver injury and death and it is important to have appropriate labeling to inform users of the risk of injury. While the submitted data may not demonstrate increasing numbers of liver injury or deaths associated with acetaminophen use annually, the number of cases of liver injury or deaths reported each year with acetaminophen use is not acceptable. The analyses included in the submission have

the same limitations as the databases discussed in the proposed rule. Furthermore, our AERS database continues to include many reports of liver injury associated with acetaminophen use each year.

Other information supports our determination. Since the publication of the 2006 proposed rule, a study (Ref. 13) was published with data that raises concern about the number of cases of acetaminophen-related liver injury. This study was a prospective population-based surveillance program in eight counties in metropolitan Atlanta over a period of five years (2000-2004) and is the first population based study of acute liver failure conducted in the United States. In this study, 94 patients were hospitalized with acute liver failure, but only 65 of the patients were included in the study. The remaining subjects refused to participate or could not be contacted following hospital discharge. Of the 65 patients, 49 were adults and 16 were children. Of the 49 adults in this study, 29 (41 percent) were identified as having acetaminophen-related acute liver failure, suggesting that acetaminophen is the most common cause of acute liver failure in adults. Of these 29 adults, 45 percent were intentional overdoses, and 55 percent were unintentional. The data were used to calculate an annual acute liver failure rate of 5.5 cases per million individuals in metropolitan Atlanta. By extrapolating this incidence rate to the entire U.S. population, the study authors estimate that approximately 1,600 cases (1200 adult cases, 400 child cases) of acute liver failure occur each year. This could result in approximately 640 cases of acute liver failure (350 unintentional) associated with acetaminophen use in the United States each year. We believe this study further justifies the need for the proposed liver warning.

Another recent study raises concerns about the ability of acetaminophen to cause liver function test abnormalities. The study was a prospective, blinded, randomized, parallel group study involving 145 subjects (Ref. 14). The subjects were divided into the following five groups,

which were roughly equal in size:

(1) Placebo

(2) Acetaminophen

(3) Acetaminophen + oxycodone

(4) Acetaminophen + hydromorphone

(5) Acetaminophen + morphine

Each acetaminophen group took 4 grams acetaminophen daily for 14 days. Thirty-one to forty-four percent of the subjects in each of the acetaminophen groups had a maximum increase in ALT values of three times the upper limit of normal. Enzyme levels returned to normal when acetaminophen was stopped. The subjects in the placebo group did not have elevated ALT values. This study demonstrates that healthy individuals using the maximum dosage amount of OTC acetaminophen can experience abnormalities of liver function tests. The clinical significance of the abnormalities is not known at this time.

All of the data available concerning acetaminophen use and liver injury suggest that there are some consumers at risk for liver injury. Based on this data, we believe it is important to warn consumers about the potential for liver injury. We will consider revising the warning if we become aware of data better defining the risk factors for acetaminophen-induced liver injury.

2. Introductory Sentence of Liver Warning

One submission (Ref. 1) disagrees with our proposal to use the term "severe" to qualify liver damage in the introductory sentences of the liver warning: "This product contains acetaminophen. Severe liver damage may occur if you take. . ." The submission argues that use of modifiers such as "severe" must be consistently applied to all OTC drug products. The submission points out that such a modifier is not used in the language of the proposed stomach

bleeding warning on OTC NSAID products, where the submission argues it would be more appropriate. This submission also requests that we modify the introductory sentences of the liver warning to be clearer that liver injury results from using more than the recommended dose of acetaminophen (overdose), and to state situations to avoid that may result in using too much acetaminophen.

The submission recommends three versions of the liver warning that are similar to the warning in the 2006 proposed rule: one for adults, one modified for children under 12 years of age[3], and one for adults and children under 12 years of age[4]. The modified liver warning language proposed in the submission for adults reads as follows:

> "Liver warning: This product contains acetaminophen. Liver damage may occur if you take more than the recommended dose (overdose).
>
> Do not:
>
> take more than 8 caplets in 24 hours
>
> use with other drugs containing acetaminophen"

We disagree with the comment in the submission regarding the word "severe" and believe it is appropriate in the liver warning. The data and information described in the 2006 proposed rule to support the need for this warning indicate that acetaminophen-induced liver injury can often be serious, even fatal. As we state in the 2006 proposed rule (71 FR 77314 at 77316), acetaminophen-related liver injury led to approximately

- 56,000 emergency department visits (1993-1999),

[3]For products labeled for children under 12 years of age only, the first bullet of the modified warning reads, "give the child more than 5 doses in 24 hours."

[4]For products labeled for adults and children under 12 years of age, the first bullet of the modified warning reads, "give the child more than 5 doses in 24 hours", the second bullet reads "take more than 8 caplets in 24 hours." The third bullet reads "with other drugs containing acetaminophen."

- 26,000 hospitalizations (1990-1999), and
- 458 deaths (1996-1998).

Of these cases, unintentional acetaminophen overdose was associated with

- 13,000 emergency department visits (1993-1999),
- 2189 hospitalizations (1990-1999), and
- 100 deaths (1996-1998) (71 FR 77314 at 77318).

In addition, as discussed in section IV.A.1. of this document, we have recent data suggesting that acetaminophen may be the most common cause of acute liver failure in the United States (Ref. 13). Therefore, we believe that the word "severe" is appropriate in the liver warning. In addition, we agree with the submission that the word "severe" is also appropriate in the stomach bleeding warning on OTC NSAID products. Therefore, we are requiring that the introductory sentences of the stomach bleeding warning be revised to include the word "severe" (see section V.A. of this document).

We are not going to include the word "overdose" in the introductory sentences of the liver warning as the submission suggests because we are not sure whether consumers will understand the term "overdose" in this case. We believe that consumers typically relate "overdose" to deliberate overdose (i.e., suicide) or unintentional overdose of illegal drugs used for recreational purposes. We do not think that consumers will understand "overdose" in the liver warning to mean "exceeded the recommended dose." However, we are going to modify the liver warning as the submission requests to be clear that consumers should not use more than the recommended dose of acetaminophen. We are making this modification in the first bulleted statement instead of the introductory text (see section IV.A.3. of this document).

3. First Bulleted Statement: Maximum Safe Daily Dose of Acetaminophen

One submission requests that we consider stating in the liver warning that using the maximum daily dose of 4 grams for five or more consecutive days could cause severe liver injury (Ref. 11). Another submission requests that we modify the liver warning language to more clearly state that liver injury from acetaminophen results from using more than the recommended dose (Ref. 1).

We are not modifying the wording of the first bulleted statement in the liver warning to advise that liver injury can occur from using 4 grams acetaminophen daily for five or more consecutive days. The submission does not include any data to support this recommendation. A study discussed previously (Ref. 15) demonstrated asymptomatic elevations of liver function tests in healthy subjects after receiving 4 grams of acetaminophen for several days. As we noted, the clinical significance of these test abnormalities are unclear at this time and additional study is needed. We are interested in any data that may allow us to better assess how the risk of liver injury increases with increasing number of days of acetaminophen use. If we become aware of such data, we will consider revising the liver warning at that time.

We are modifying the first bullet of the liver warning to more clearly advise consumers that liver injury may occur from using more than the recommended dose of acetaminophen. In this document, we are revising the first bulleted statement of the liver warning for adults[5,6] to read:

- more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount

[5]For products labeled for children under 12 years of age only, the first bulleted statement of the liver warning reads, "[bullet] child takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount."

[6]Products labeled for adults and children under 12 years of age contain two bulleted statements regarding the recommended daily dose. The first bulleted statement of the liver warning reads, "[bullet] adult takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount [bullet] child takes more than [insert maximum number of daily dosage units] in 24 hours, which is the maximum daily amount."

Although this revised bulleted statement is longer than the statement in the 2006 proposed rule, we believe consumers will be more likely to understand that the risk of liver injury increases if they exceed the maximum daily dose.

4. Second Bulleted Statement: Concomitant Use

In this document, we are requiring two concomitant use warnings: (1) the second bullet of the liver warning and (2) the "Do not use" warning (see section IV.B. of this document). Both were included in the 2006 proposed rule. As discussed in the 2006 proposed rule, we believe that simultaneous use of multiple acetaminophen-containing drug products is a strong risk factor for liver injury caused by exceeding the recommended daily dose of acetaminophen. The second bulleted statement of the proposed liver warning cautions consumers about using more than one product containing acetaminophen at a time (see section IV.A. of this document). We are including the same language for this warning as included in the 2006 proposed rule. This language is supported by four submissions stating the importance of this warning without suggesting any modification (Refs. 1, 2, 10, and 11). We did not receive any submission suggesting any modifications.

5. Third Bulleted Statement: Alcohol Warning

In this document, we are requiring the alcohol warning included in the 2006 proposed rule. We are including it as the third bulleted statement of the liver warning as proposed. It advises consumers that severe liver injury may occur if they take 3 or more alcoholic drinks while using acetaminophen drug products. We have considered the data discussed in the proposed rule and new data submitted to us, including recent clinical studies. We do not believe the new data demonstrate that alcohol users have the same risk for liver injury as non-users of alcohol. Therefore, we are requiring the alcohol warning as part of the liver warning because

they are interrelated and are more likely to be understood as a single warning than as separate warnings.

In the 2006 proposed rule (71 FR 77314 at 77329), we discuss a prospective clinical study in which 275 individuals were identified as developing acute liver failure due to acetaminophen use during a 6-year span at 22 centers (Ref. 15). Of these individuals, those who abused alcohol had median acetaminophen blood levels that were half as much as those who did not abuse alcohol ($p = 0.003$). The investigators found that the subjects with acute liver failure who reported taking 4 grams or less of acetaminophen daily were often alcohol abusers (65 percent). The investigators also found that patients with acute liver failure who were taking more than 4 grams acetaminophen daily consumed less alcohol than those who took less than 4 grams acetaminophen daily. The patients who used alcohol reported using less acetaminophen daily than the patients who did not use alcohol. The investigators commented that alcohol may be an important risk factor for acute liver failure in the subjects taking 4 grams or less of acetaminophen daily.

In the proposed rule, we also discussed retrospective data from our AERS database that suggest the same conclusion (71 FR 77314 at 77320 to 77321). Of the 132 individuals identified in this database as developing liver disease after using acetaminophen, alcohol users had used less acetaminophen than those who did not use alcohol (5.6 grams for users vs. 6.9 grams for non-users). Of the 65 individuals identified as developing severe liver disease after using acetaminophen, where dosing information was available, alcohol users had used less acetaminophen than those who did not use alcohol (6.0 grams for users vs. 8.6 grams for non-users). These data suggest that lesser amounts of acetaminophen may cause liver damage in people who use alcohol compared to those who do not.

After publication of the 2006 proposed rule, we received five submissions concerning the alcohol warning (Refs. 1, 4, 10, 11, and 12). Four of the five submissions support the proposed alcohol warning, and one does not. Two of these four submissions (Refs. 11 and 12) argue that the prospective clinical study discussed in the 2006 proposed rule (Ref. 15) supports the occurrence of liver injury in consumers who use OTC acetaminophen and consume alcohol. One of these submissions (Ref. 12) cites three clinical case series suggesting an association between alcohol use and unintentional acetaminophen-related liver injury (Refs. 16, 17, and 18). In these case series, between 14 and 40 percent of the cases involved individuals consuming OTC acetaminophen doses (i.e., no more than 4 grams daily). The submission also cites mechanistic studies suggesting that regular alcohol use may significantly alter the metabolism of acetaminophen, leading to liver injury.

The submission that objects to the warning states that an alcohol warning for OTC acetaminophen drug products is not necessary because individuals with a history of alcohol use can safely use the maximum daily dose of acetaminophen (Ref. 1). The submission argues that current scientific data suggest that the risk of acetaminophen-related liver injury is associated with using more than the maximum OTC daily dose of acetaminophen, irrespective of alcohol use. While we had previously reviewed much of the submitted data in preparing the 2006 proposed rule, there are some studies that were submitted that we had not previously reviewed. As described in section IV.C. of this document, we believe the most clinically meaningful of these studies are the prospective clinical studies. Therefore, our review in this section focuses on these studies.

There are six prospective, double-blinded, randomized, placebo-controlled studies designed to evaluate whether maximum therapeutic doses of acetaminophen (4 grams daily)

cause liver injury in alcoholic patients (Ref. 1). Four studies were coordinated by the Rocky Mountain Poison and Drug Center (RMPDC) and are similar in design to each other. These studies involved acetaminophen use (4 grams daily) for 2, 2, 3, and 5 days, respectively. The fifth study, a 4-day study, was of similar design but is available only as an abstract. Therefore, we did not consider this study in our evaluation. The sixth study enrolled subjects who used 4 grams of acetaminophen daily for 10 days.

We discussed both 2-day studies in the 2006 proposed rule. Although neither revealed liver injury, we stated that they did not "provide reliable evidence that people with chronic alcohol use can safely take 4[grams]/day of acetaminophen, particularly for up to 10 days in accordance with OTC drug product labeling" because of study design limitations (71 FR at 77314 at 77336). The major limitations were that the duration of acetaminophen use was not long enough (i.e., not 10 days) and the liver function exclusion criteria did not allow subjects with AST and ALT values above certain levels. Therefore, we could not draw conclusions about alcohol and acetaminophen use from these studies.

The 3- and 5-day studies were designed to address the limitations of the two-day studies. They enrolled chronic heavy alcohol users entering alcohol detoxification facilities. A total of 372 subjects completed the 3-day study, and 130 subjects completed the 5-day study. The submission argues that these patients represent the alcohol users at greatest risk for liver injury when using acetaminophen. The study subjects had AST and ALT $\leq$200 IU/L and INR $\leq$1.5 which expanded the population and included more alcoholic subjects than the two-day studies. The primary endpoint was liver function tests. There were not any statistically significant differences in liver function tests after acetaminophen use. Therefore, the studies did not reveal signs of liver injury when using OTC acetaminophen for 3 or 5 days.

The other prospective study enrolled 150 subjects who consumed one to three alcohol drinks daily and took 4 grams acetaminophen or placebo daily for 10 days (Ref. 19). The primary endpoint was liver function testing (ALT, AST, total bilirubin, alkaline phosphatase, and total protein) at days 0, 4, and 11. There were no changes in liver function in the placebo group on days 4 or 11 compared to day 0. There were no changes in liver function in the acetaminophen group on day 4 compared to day 0. However, there was a statistically significant increase in ALT in the acetaminophen group on day 11 compared to day 0. Of the 100 subjects in the acetaminophen group that had elevated ALT values, the ALT was 1 to 3 times the upper limit of normal for 19 subjects, 3 to 5 times the upper limit of normal for 1 subject. There was also a rechallenge in 10 subjects (one placebo and nine acetaminophen) showing similar results, except ALT increases on day 11 were slightly smaller. These changes in ALT blood levels are similar to those observed in healthy subjects (Ref. 15) when given 4 grams of acetaminophen daily. The clinical significance of these findings is not apparent at this time.

We do not believe the new studies justify removal of the alcohol warning. We cannot draw conclusions from these new studies for numerous reasons. First, only one of the studies involves the maximal OTC acetaminophen use (i.e., 4 grams daily for 10 days). Second, the number of subjects enrolled in the studies is small. The largest number of subjects using 4 grams acetaminophen daily was 258 subjects in the 3-day study. The one study involving the maximal OTC acetaminophen use (i.e., 4 grams daily for 10 days) only enrolled 150 subjects. With these sample sizes, it is possible that significant changes in liver function would not be detected. It is difficult to use these studies as evidence to demonstrate that a specific population is not at increased risk for liver injury. Third, there are a significant percentage of alcohol users in the various liver injury databases. This may only represent a small percentage of the overall

population of users and, as such, will make it difficult to understand all of the factors that may have contributed to their developing liver injury. Many of them are reported to have developed liver injury with doses close to the current daily recommended dose. Until we have a better understanding of the mechanism in these individuals, studies such as those submitted to us and discussed in this document will not be adequate to establish the safe dose of acetaminophen in all alcoholics. Fourth, the studies were not open for enrollment to a representative population of all people who use alcohol. The population of alcohol users is not homogenous and all are not represented in these studies. Alcohol users will have variable degrees of underlying alcohol related liver injury and variable ability to metabolize acetaminophen. As a consequence, it is difficult to generalize the results of these studies to all people who use alcohol. Additional research needs to be conducted to better understand why people who use alcohol make up a disproportionate percentage of subjects in the liver injury databases and determine what dose adjustment may be considered for this population.

Because these new studies do not adequately demonstrate that alcohol use is not a risk factor for acetaminophen-induced liver injury, we believe an alcohol warning continues to be necessary. An alcohol warning has been required on acetaminophen products since 1999. There has been a concern for a long time of the increased risk to regular users of alcohol. We describe numerous data in the 2006 proposed rule (summarized earlier in this section of the document) that suggest alcohol use may increase the risk of acetaminophen-induced liver injury. The studies provided in the submission are not adequately designed to dismiss the previously available data. Very large safety studies are needed to better establish the risk for liver injury, the safe dose of acetaminophen in this population and identify subpopulations within alcohol users who may be at the greatest risk for liver injury.

The submission that argues against requiring the alcohol warning also suggests a modified warning (Ref. 1). The submission states that, if we continue to believe that an alcohol warning is necessary, then the warning should be separated from the liver warning and read as follows:

> 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. Taking more than the recommended dose (overdose) of acetaminophen may cause liver damage.

The submission argues that we do not provide evidence to support our rationale for incorporating the alcohol warning as part of the liver warning. The submission argues that combining the two warnings will mislead and confuse consumers. The submission also argues that its suggested alcohol warning language better reflects the available scientific evidence, which demonstrates that the risk of acetaminophen-induced liver injury is not affected by alcohol use.

We disagree with the submission. We are requiring the proposed alcohol warning as the third bullet of the liver warning. We continue to believe that the two warnings are interrelated and combining the two warnings will be less confusing to consumers than separating the two warnings. The warning proposed by the submission suggests that liver injury in alcohol users occurs only with doses greater than 4 grams per day. We have clinical reports of liver injury in people who use alcohol at doses very close to 4 grams per day. As a consequence, we are not in a position now to state that liver injury only occurs with doses greater than 4 grams per day.

B. Concomitant Use Warning

We are requiring a separate concomitant use warning under the “Do not use” subheading

in addition to the concomitant use warning included as part of the liver warning (see section IV.A.4. of this document). Both warnings advise consumers to avoid using multiple acetaminophen-containing drug products at the same time. The "Do not use" warning also advises consumers to consult a doctor or pharmacist if consumers do not know whether a drug product contains acetaminophen.

We are revising the proposed warning included in the 2006 proposed rule, which reads, "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" (proposed 21 CFR 201.325(a)(1)(iii)(B)). In this document, the first sentence is the same, but the second sentence reads, "If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist." We received one submission proposing this modified wording (Ref. 1). The submission states that the meaning of our proposed second sentence is unclear. We agree with the submission. We believe the revised sentence is clearer than the proposed sentence without making the sentence significantly longer. Therefore, the revised warning appears in 21 CFR 201.326(a)(1)(iii)(B) of this document.

C. Liver Disease Warning

In this document, we are requiring the liver disease warning included in the 2006 proposed rule. This warning advises consumers with liver disease against using acetaminophen unless directed by a doctor. As discussed in the 2006 proposed rule, we proposed the liver disease warning primarily because we identified cases from our AERS database and the Multiple Cause of Death Files suggesting that chronic liver disease may be a risk factor for developing or increasing the severity of liver injury when using acetaminophen (71 FR 77314 at 77328 to 77329). We also cite acetaminophen metabolism studies suggesting that consumers with liver

disease may be at higher risk of producing the toxic metabolite NAPQI than consumers without liver disease.

Since publication of the 2006 proposed rule, we received and reviewed additional data and information concerning OTC acetaminophen use by consumers with liver disease (Refs. 1, 11, and 12). After reviewing these data, we still have concerns that some people with underlying liver disease are at higher risk for liver injury with acetaminophen. Therefore, we are requiring the proposed liver disease warning because we believe it is necessary to alert consumers with liver disease that they should ask a doctor before using acetaminophen. The required warning for products labeled only for adults reads: "Ask a doctor before use if you have liver disease." We are requiring similar warnings for products labeled for children under 12 years of age[7] and for products labeled for adults and children[8].

In response to the 2006 proposed rule, we received three submissions containing data and information concerning the liver disease warning, including over 200 studies (Refs. 1, 11, and 12). Two of the three submissions support the need for the liver disease warning (Refs. 11 and 12). Both argue that the proposed liver disease warning is based on sound scientific data. The submissions reference data presented in the 2006 proposed rule as well as acetaminophen metabolism studies suggesting that consumers with liver disease metabolize acetaminophen differently. One of the submissions, from the American Association for the Study of Liver Disease (AASLD), cites its "Practice Guideline on Treatment of Chronic Hepatitis C" as supporting the proposed warning. According to the guideline, patients with chronic hepatitis C (a form of liver disease) should be treated with a maximum daily dose of 2 grams rather than the

[7]The warning for products labeled for children under 12 years of age reads: "Ask a doctor before use if the child has liver disease".

[8]The warning for products labeled for adults and children reads: "Ask a doctor before use if the user has liver disease."

OTC labeled maximum daily dose of 4 grams.

The third submission (Ref. 1), from a manufacturer of acetaminophen, argues that data demonstrate the proposed liver disease warning is not needed. The submission contends that liver disease is not a risk factor for developing liver injury with OTC doses of acetaminophen and that the data cited in the 2006 proposed rule do not support the need for the liver disease warning. The submission proposes the following hierarchy of data, going from the highest to lowest level of evidence:

1. Data revealing clinical outcomes following acetaminophen use
2. Human acetaminophen metabolism studies
3. Human acetaminophen metabolism studies using probe molecules (e.g., chlorzoxazone)
4. In vivo animal studies
5. In vitro cellular studies
6. Studies using surrogate markers for acetaminophen metabolism (e.g., plasma glutathione levels)

It should be noted that clinical outcome refers to liver function testing, acute liver failure, liver transplant, death, etc. Although the submission includes studies from all levels of this hierarchy, it emphasizes the importance of the studies with clinical outcomes over all other studies. According to the submission, these studies do not reveal any evidence of an adverse outcome when consumers with liver disease use acetaminophen, meaning none of the study subjects developed liver failure, and liver function tests did not suggest liver injury.

We focused our review on the data with clinical outcomes. We received five clinical studies:

- Benson 1983 (Ref. 20)
- Andreasen 1979 (Ref. 21)
- McNeil 2007 (Ref. 1)
- Green 2005 (Ref. 22)
- Dargere 2000 (Ref. 23)

Throughout the remainder of this section, we discuss the three of the five clinical studies. We do not discuss the Green 2005 and Dargere 2000 studies because, although these two studies do not reveal different clinical outcomes for consumers with or without liver disease who use OTC acetaminophen, we do not have complete study reports for these studies. Therefore, we cannot draw any conclusions based on abstracts for these two studies.

Before describing the studies with clinical outcomes, we should note that we also considered the second level of evidence (human acetaminophen metabolism studies) in the proposed hierarchy. We believe these studies may be meaningful in determining whether liver disease is a risk factor for liver injury when using OTC acetaminophen. We received 26 acetaminophen metabolism studies (Ref. 1), but could not draw conclusions from them because of a number of limitations. Only 13 of the 26 studies examined the levels of acetaminophen and its metabolites (e.g., glutathione, sulfate, and thiol metabolites) in the blood after subjects take acetaminophen. We agree that knowing the level of acetaminophen in a person's blood alone does not necessarily improve our understanding of acetaminophen metabolism in consumers with liver disease as it relates to an increased risk for acetaminophen- induced liver injury. Of those 13 studies that include acetaminophen metabolites, only one study involved multiple doses of acetaminophen. The multiple-dose study included consumers with liver disease who used 4 grams acetaminophen daily for 4 days. None of the metabolism studies included study subjects

who used acetaminophen for the maximum OTC labeled dose (i.e., 4 grams daily for 10 days). We cannot draw conclusions about the risk for liver injury due to acetaminophen from the human acetaminophen metabolism studies.

The submission from the acetaminophen manufacturer provides additional data for the Benson 1983 study that we cite in the 2006 proposed rule (71 FR 77314 at 77328 to 77329). We stated that the study shows no difference in liver function test results for consumers with liver disease who used 4 grams acetaminophen daily for 13 days as compared to consumers with liver disease who used a placebo for 13 days. We stated that the small sample size of 20 subjects with liver disease and cross-over study design prevent us from drawing conclusions from the study. The submission argues that the cross-over study design is adequate and not a limitation. We now agree that the crossover design may not be a major study limitation. The number of subjects, however, is small and do not allow for broad conclusions in the entire population of people with underlying liver disease. Therefore, this study does not provide sufficient data from which to conclude that four grams per day is a safe dose for all patients with underlying liver disease.

The submission also included the Andreasen 1979 study that we cite in the 2006 proposed rule (71 FR 77314 at 77328 to 77329). We cited this study as evidence of altered acetaminophen metabolism in consumers with liver disease. The study enrolled 4 subjects with liver disease (cirrhosis) and 9 control subjects receiving multiple doses of acetaminophen or placebo. Study subjects were given 3 grams acetaminophen or placebo daily for 5 days. Liver function tests were conducted on the study subjects. These tests did not suggest any difference in liver function between the control subjects and those with liver disease, although the study did show prolonged clearance of acetaminophen in patients with liver disease. It is difficult to draw any conclusions from this small study.

An unpublished 2007 study included in the submission that was conducted by a manufacturer of acetaminophen enrolled 12 subjects with liver disease (cirrhosis) who used 4 grams acetaminophen daily for 4 days (one dose on day 5). The liver function test results after using acetaminophen did not differ from those before using acetaminophen. This study does not provide sufficient information to make any conclusions regarding the safe dose of acetaminophen or the risk of liver injury in users with chronic liver disease.

Limitations of the studies prevent us from drawing any conclusions about the safety of acetaminophen use in patients with liver disease using 4 grams acetaminophen over 10 days. The two most significant limitations are the small number of study subjects and the duration of acetaminophen use. The three clinical studies only enrolled a total of 36 subjects with liver disease. Two of the studies only involved acetaminophen use for 4 or 5 days. The lack of liver injury or signs of liver injury in these studies does not mean that the same results would be seen in studies enrolling larger numbers of subject using acetaminophen for longer periods of time.

Although these prospective clinical studies are inconclusive, the retrospective data cited in the 2006 proposed rule suggest that consumers with liver disease may be at increased risk for liver injury when using OTC acetaminophen. As discussed in the 2006 proposed rule, we identified a total of 282 adult cases of liver injury associated with acetaminophen in our AERS database between January 1998 and July 2001. A history of prior liver disease, or possible underlying liver disease, was reported in 70 cases (25 percent). Among the 70 cases with liver disease, 49 percent developed severe liver injury.

We also reviewed the Multiple Cause of Death Files between 1996 and 1998. These death certificates showed that unintentional acetaminophen overdose was associated with an annual average of 100 deaths. In these deaths, the presence of chronic liver disease was reported

in 61 percent of the unintentional acetaminophen overdose cases. The high prevalence rate of liver disease from these two databases (25 and 61 percent) suggests that liver disease increases the risk of liver injury when using acetaminophen because only 2 to 3 percent of U.S. adults have chronic liver disease (Ref. 24) . The fact that people with underlying liver disease make up a disproportionate percent of the cases of severe liver injury relative to its prevalence in the general population suggests that there is a higher risk for persons with liver diseases. It is difficult to refute this type of data without conducting larger studies with repeated exposures over an extended period time.

Based on this data, we believe that it is appropriate to advise consumers with liver disease to ask a doctor before using acetaminophen because they may be at risk for developing more serious liver injury. We also agree with the second submission (Ref. 11) that the warning is appropriate because it will advise liver disease patients about a potential risk of further liver injury without advising them to avoid using acetaminophen or limiting use to a pre-determined dose. The submission states that such an open-ended warning will permit healthcare providers to advise their liver disease patients on a case-by-case basis. We plan to continue to require the warning unless and until we become aware of adequate studies demonstrating that consumers with liver disease are not at risk for liver injury when using OTC acetaminophen or we obtain additional information that may be more informative in providing dosing recommendations.

D. Drug Interaction Warning

In this document, we are requiring a warning on OTC acetaminophen drug products about a potential drug-drug interaction between acetaminophen and warfarin. We did not specifically propose this type of warning in the December 2006 proposed rule because we thought that the data available at the time did not demonstrate the need for such a consumer

warning. The proposed rule did, however, request comments and data concerning the need for a drug-drug interaction warning on OTC acetaminophen drug products. Since the publication of the December 2006 proposed rule, we have determined that a consumer drug-drug interaction warning is needed based on the current data and information available to us.

As stated in the proposed rule (71 FR 77314 at 77338), labeling for warfarin-containing prescription drug products lists acetaminophen as a drug that can increase warfarin's anticoagulant effect. The proposed rule also discussed data concerning the potential drug-drug interaction between acetaminophen and warfarin:

- 20 bleeding adverse events (3 probable and 17 possible) reported by consumers using warfarin and acetaminophen concurrently in our AERS databases
- Numerous clinical studies examining the ability of acetaminophen to interact with warfarin by measuring tests of blood clotting
- Two studies examining the mechanism of a drug interaction between acetaminophen and warfarin.

We stated that we believe that the actual numbers of bleeding events may be much higher than reported in our AERS database because adverse events are significantly underreported. We stated that the results of studies measuring coagulation tests were conflicting with regard to the effect of acetaminophen on warfarin anticoagulation. At that time, we thought we could not draw firm conclusions from these studies on which to base a consumer warning because they did not control for other factors that may affect warfarin anticoagulation in consumers using warfarin (e.g., vitamin K use). We also stated that the mechanism of the potential drug-drug interaction is unknown. Because we thought that the currently available data did not demonstrate sufficient evidence to warrant a consumer warning, we requested comment and data from the public on this

issue to gather more information.

In response to our request, we received two submissions (Refs. 11 and 12). Both submissions state that we should require a warning to ask a doctor before using OTC acetaminophen if using warfarin. They provide the following data to support their request:

- A prospective study examining the effect of acetaminophen in consumers on warfarin therapy
- Retrospective data on the use of acetaminophen by consumers on warfarin therapy
- Articles examining the mechanism of an interaction between acetaminophen and warfarin.

In addition, one of the submissions (Ref. 11) argues that drug-drug interaction warnings are also needed on OTC acetaminophen for phenobarbital and isoniazid, but does not include any data to support this request. We found one reference source that noted the risk for liver injury may be increased in people taking isoniazid or phenobarbitol if they take more than the recommended dose of acetaminophen (Ref. 25). However, since we are already warning people not to use more than the recommended amount of acetaminophen, we are not requiring a warning about the potential drug-drug interaction between phenobarbital or isoniazid.

After reviewing the data, we believe it demonstrates that consumers using acetaminophen with warfarin may increase their International Normalized Ratio (INR), which may serve as a sign of increased risk for bleeding. This conclusion is based primarily on the submitted prospective study (Ref. 26) and another prospective study (Ref. 27) that we identified from the published literature.

The retrospective data include a case report of a 74-year old man on warfarin therapy who experienced an abrupt increase in INR after using acetaminophen (Ref. 28). INR returned

to normal after stopping the acetaminophen. There is another case report of 81-year old woman whose INR reached 16, leading to bleeding, after using acetaminophen (Ref. 29). The other retrospective data consists of medical records from 1,093 patients on warfarin therapy over a 5 year period (Ref. 30). The records show that 316 (29 percent) of these patients experienced increased INR when using acetaminophen and warfarin at the same time. These data suggest that OTC acetaminophen may increase the anticoagulation effect of warfarin, although other factors that may affect coagulation (e.g., vitamin K use) were not controlled for and the acetaminophen dosing was unknown. Similarly, the studies examining the mechanism of this potential drug-drug interaction speculate on possible mechanisms of interaction between acetaminophen and warfarin, although they do not clearly demonstrate the mechanism (Refs. 31, 32, and 33).

The submitted prospective study was a randomized, double-blinded, placebo-controlled, cross-over study (Ref. 26). In the study, 18 consumers on chronic warfarin therapy were given 4 grams of acetaminophen or placebo for 14 days. The two 14-day treatment periods were separated by a 2-week wash-out period. The mean INR at the beginning of the treatment periods for placebo and acetaminophen were similar (2.31 ± 0.31 and 2.25 ± 0.33, respectively). Only a modest increase in the maximum INR compared to baseline was observed when the subjects took placebo (mean maximum INR = 2.66 ± 0.73). A significant increase in the maximum INR over baseline was observed when the subjects took acetaminophen (mean maximum INR = 3.45 ± 0.78). Therefore, this study suggests that acetaminophen (4 grams daily for 2 weeks) increases the anticoagulation action of warfarin.

The second prospective study was a randomized, double-blinded, placebo-controlled study (Ref. 27). In this study, 36 subjects on chronic warfarin therapy were randomly assigned

to three groups: (1) 2 grams acetaminophen daily, (2) 4 grams acetaminophen daily, or (3) placebo. The subjects took acetaminophen or placebo for four weeks. The primary end point of this study was difference in the mean INR at weekly intervals, and the secondary end point was mean serum liver enzymes at weekly intervals. The baseline mean INR in all groups was similar (2.4 ± 0.3, 2.5 ± 0.2, and 2.5 ± 0.3). The mean INR of the placebo group did not change during the 4 weeks of the study. The 2 gram acetaminophen group reached the highest mean INR at week 2 (3.1 ± 0.5). The 4 gram acetaminophen group reached the highest mean INR at week 3 (3.4 ± 0.7). Both of these increases in INR were statistically significant compared to placebo ($p < 0.05$). There were no statistically significant differences in liver enzyme levels in the acetaminophen groups at any time during the 4 weeks. Therefore, this study suggests that acetaminophen (2 or 4 grams daily for 4 weeks) modestly increases the anticoagulation action of warfarin.

Both studies demonstrate increases in INR when using acetaminophen and warfarin at the same time. In addition, the case report of bleeding in the 81-year old woman with an INR of 16 supports the need for the warning on the prescription labeling. We believe these data also support the need for a consumer labeling statement for OTC acetaminophen about the potential for interaction between warfarin and acetaminophen, and we are including a warning statement in this final rule. We are primarily concerned with the chronic use of acetaminophen in patients using warfarin. These are patients who use acetaminophen regularly for chronic pain from conditions, such as osteoarthritis or fibromyalgia.

Typically, patients receiving warfarin undergo monthly testing of their INR. As noted in one of the interaction studies, the peak effect is noted after 2 or 3 weeks depending on the dose of acetaminophen. Thus, an increase in INR is likely to be detected during the monthly check of

the INR. Therefore, a drug-drug interaction warning for coadministration of acetaminophen with warfarin is important to educate healthcare providers and consumers about the possible interaction between these two drugs and to consider this as a possible cause of an increase in INR for patients on warfarin. The warning reads as follows: "Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin" (21 CFR 201.326(a)(1)(iii)(D)). This warning is required on all OTC acetaminophen products except those also containing NSAID(s). Combination products containing acetaminophen and NSAID(s) are required to include a warning about blood thinning drugs under the stomach bleeding warning for NSAIDs. It would be unnecessarily redundant to include the same warning under the "Ask a doctor or pharmacist before use" heading. We believe the warning will encourage patients on chronic warfarin therapy to ask their doctor about the use of acetaminophen with the warfarin and remind healthcare providers to consider this interaction when evaluating elevated INRs in their patients.

E. Warnings for Certain Sub-Populations

1. Warning for Consumers Infected With Human Immunodeficiency Virus (HIV)

In this document, we are not adding any warning that HIV-infected consumers are at increased risk of liver injury when using acetaminophen. We reached this conclusion after reviewing the available data on the use of acetaminophen by HIV-infected individuals. We find the currently available data do not adequately demonstrate that acetaminophen, when used according to the OTC label (i.e., maximum daily dose of 4 grams for no longer than 10 days), poses risk for HIV-infected individuals.

In the 2006 proposed rule, we requested comments and data on whether the maximum daily dose (4 grams) of acetaminophen is unsafe for HIV-infected consumers (71 FR 77314 at 77337 to 77338). As discussed in the proposed rule, this safety concern stems from a citizen

petition that makes the following arguments to support the need for an HIV warning:

- 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 people with HIV disease, and acetaminophen may further reduce survival by depleting GSH.

After submission of the petition, we received a submission from a manufacturer of OTC acetaminophen products arguing that an HIV warning is unnecessary (Ref. 1). The submission included numerous in vitro and in vivo studies both supporting and refuting that HIV-infected patients are at increased risk of liver injury when using acetaminophen.

In the proposed rule, we did not propose an HIV warning because there was not adequate data demonstrating that use of acetaminophen decreased the survival rate of HIV-infected consumers. In vitro and in vivo studies did demonstrate low levels of GSH and its precursors in HIV-infected consumers, suggesting the toxic acetaminophen metabolites may accumulate in these individuals. However, we were not aware of any data demonstrating that these low levels of GSH are clinically meaningful (i.e., impact survival or increase acetaminophen liver injury). In vitro studies also demonstrated that N-acetylcysteine, which is used to treat acetaminophen overdoses, improved the performance of T cells from healthy and HIV-infected individuals. However, these studies did not demonstrate that the increased GSH levels in HIV-infected individuals after N-acetylcysteine treatment lead to improved survival.

Although many of the studies did not demonstrate clinically meaningful effects of low GSH levels in HIV-infected individuals, as stated in the proposed rule, we did review clinical studies demonstrating the relationship between GSH levels and survival. We could not conclude

that decreased GSH levels in HIV-infected individuals lead to decreased survival rates because of the following deficiencies:

- No clear description of the study design
- Survival data were not collected for 17 percent of the study population
- No baseline characteristics provided for individuals participating in the clinical trial
- No documentation of antiviral treatment or concomitant use of other medications
- N-acetylcysteine administration was not randomized

We also could not find any hepatic adverse events in the AERS database associated with HIV infection and acetaminophen use.

In response to the request for data and comment in the proposed rule, we received three submissions regarding an HIV warning. Two submissions argue that currently available data do not support the need for an HIV warning (Refs. 1 and 11). The third submission argues that we should require an HIV warning (Ref. 12). All three submissions cite in vitro and in vivo data to support their arguments. However, the only data that demonstrate a clinically meaningful adverse effect of acetaminophen use by HIV-infected individuals are two case reports. The remaining studies examine the relationship of GSH and acetaminophen metabolites levels in HIV infection. Some of the studies demonstrate a correlation between GSH and acetaminophen metabolites levels and HIV infection, while others do not. Regardless of the study results, these studies do not provide us with evidence that the HIV-infected patients experience liver injury when using acetaminophen.

There are case reports of two HIV-infected individuals experiencing liver injury after consumption of therapeutic doses of acetaminophen (i.e., less than or equal to 4 grams daily). We cannot conclude that HIV-infected individuals are at higher risk of acetaminophen-induced

liver injury than uninfected individuals based on these reports. In the first report, a 45 year old HIV-infected male developed signs of severe liver injury after using 4 grams acetaminophen daily for 5 days (Ref. 35). The signs of liver injury went away after treatment with N-acetylcysteine. It is difficult to determine whether the HIV infection placed this patient at greater risk for acetaminophen liver injury because there were many other potential risk factors: chronic alcohol use, tobacco use, opiate use, malnutrition, and hepatitis B and C infection. In the second report, a 31 year old HIV-infected male was hospitalized with liver injury after using 2 grams acetaminophen on the previous day (Ref. 36). Again, there were many other potential risk factors for liver injury: alcohol abuse, malnutrition, and concomitant chronic use of zidovudine (in combination with ribavirin).

We are not requiring an HIV warning in this document because we are not aware of data demonstrating that HIV-infected patients (in the absence of other risk factors) are at greater risk of acetaminophen-induced liver injury. We will reconsider our position if new data become available.

2. Warning for Malnourished Consumers

In this document, we are not requiring any warning that malnourished consumers are at increased risk of liver injury when using acetaminophen as directed (i.e., no more than 4 grams daily for up to 10 days). By malnourished, we mean consumers who fast, have eating disorders, or whose diets do not provide a healthy minimum caloric intake for other reasons. We arrived at this conclusion after reviewing the currently available data on the use of acetaminophen by these consumers. These data do not sufficiently demonstrate that acetaminophen when used according to labeling poses an increased risk of liver injury in these individuals relative to other individuals.

We are considering this issue because, in the 2006 proposed rule, we requested comments and data on whether the maximum daily dose of acetaminophen is unsafe for individuals who have reduced glutathione levels. A small amount of acetaminophen is metabolized through a pathway that generates a potentially toxic intermediate, NAQPI. Glutathione conjugates with NAQPI and the conjugate is then excreted in the urine. Malnourished individuals have been shown to have reduced glutathione levels (Refs. 37, 38, and 39). Therefore, it is possible that low glutathione levels may increase the risk for liver injury because there would be less available to bind to NAQPI. Low glutathione levels may a surrogate for identifying a population at increased risk of liver injury with acetaminophen, but it was unclear how much of the deficiency is necessary.

In response to our request, we received three submissions regarding malnourished consumers (Refs. 1, 11, and 12). One submission (Ref. 12) argues that we should require such a warning because malnourished consumers may be at greater risk for acetaminophen-induced liver injury than other consumers. In addition, the submission recommends additional studies to further evaluate the liver injury risk for malnourished consumers. The second submission (Ref. 11) also states the need for such studies but does not discuss the need for a warning. The third submission (Ref. 1) argues that data do not demonstrate the need for a warning. The three submissions cite the following types of data to support their arguments:

- A prospective study examining the effect of fasting on acetaminophen metabolism
- Retrospective data (case reports and case report series) concerning the use of acetaminophen and liver injury in malnourished individuals
- Human studies examining the effect of fasting on glutathione levels
- Review articles on glutathione and analgesics.

After reviewing this information, we cannot make a conclusion about the risk of liver injury due to acetaminophen in malnourished individuals. In the prospective study (Ref. 40), six obese individuals were given 500 calorie diets for 5 days (group 1), and three obese individuals were given 1000 calorie diets for 13 days (group 2). The study subjects did not have a history of alcohol abuse and had normal liver and kidney function prior to study enrollment. The subjects in group one took 2 grams acetaminophen on days 1 and 5. The urine of study subjects was collected every 2 hours for 12 hours after the acetaminophen dose. The subjects in group two took 2 grams acetaminophen on days 1, 7, and 13. The urine of study subjects was collected every 2 hours for 10 hours after the acetaminophen dose. Liver tests were performed at 12, 24, 36, and 120 hours after the acetaminophen dose. The clearance of acetaminophen on day 1 in both groups was nearly identical to the clearance on subsequent days. The same is true for acetaminophen metabolites (i.e., glucouronide, sulfate, and thiols). Liver function tests remained unchanged throughout the study. This study suggests that acetaminophen metabolism is not altered in malnourished consumers. It is difficult to make any conclusions about the risk of liver injury with acetaminophen based on this data. The small sample size of this study and the intermittent dosing at less than the maximum daily dose prevents us from drawing any conclusions. Additionally, if differences in metabolism were detected, it would be difficult to assess what amount of difference was clinically meaningful.

Two submissions (Refs. 1 and 12) provide retrospective data concerning acetaminophen-induced liver injury in malnourished consumers. The first retrospective data is a case series report describing liver injury caused by acetaminophen overdose in association with alcohol and fasting (Ref. 41). This report identifies 21 patients who developed severe liver injury when using acetaminophen. All of the patients took more than 4 grams acetaminophen daily and

nearly all were recently fasting. The study authors concluded that fasting is a risk factor for acetaminophen-induced liver injury. However, we do not believe the study supports this conclusion for OTC use of acetaminophen. All of the patients exceeded the maximum OTC acetaminophen dose of 4 grams daily, with 11 patients using more than 10 grams daily. Because the patients ingested more than the recommended amount of acetaminophen and also ingested alcohol, it is difficult to identify the contribution of fasting to the development of liver injury.

The other retrospective data consist of case reports. One submission describes relevant reports from our AERS database (Ref. 1). The database includes 20 reports of liver injury in individuals using acetaminophen who appear to be malnourished. In 17 out of 20 reports, the acetaminophen dose was not known or exceeded the maximum OTC daily dose. Only three reports concerned malnourished consumers using acetaminophen at therapeutic doses (i.e., no more than 4 grams daily). This submission also refers to a literature search that revealed 60 reports of liver injury when malnourished individuals took acetaminophen. In 44 cases, the acetaminophen dose exceeds the maximum OTC dose, and, in 11 cases, the acetaminophen dose was not reported. There were five cases of liver injury when using recommended OTC doses of acetaminophen.

There were also two published case reports submitted. The first case report (Ref. 36) describes a malnourished HIV-infected individual, who was hospitalized after using 2 grams of acetaminophen. In this case, the patient was a chronic alcohol user taking zidovudine (AZT) for HIV. The second report (Ref. 42) describes a 53 year old women who developed liver injury after using acetaminophen (4 grams) daily following a period of fasting.

Of all these cases, there are nine cases of liver injury resulting from acetaminophen use at or below 4 grams daily. Nine case reports represent a small fraction of the overall number of

case reports. Therefore, the case reports by themselves do not demonstrate that malnourished individuals are at higher risk of liver injury when using OTC acetaminophen than non-malnourished individuals.

The submitted data are not sufficient to conclude that acetaminophen used at maximum daily OTC dose (4 grams daily for 10 days) by malnourished individuals poses additional risk of liver injury in these individuals. Therefore, we are not requiring any warning for these individuals at this time. If new data become available, we will reconsider our position on this issue.

3. Warning for Consumers with Gilbert's Syndrome

In this document, we are not requiring any warning for consumers with Gilbert's syndrome. Available data do not demonstrate that acetaminophen used according to the OTC label (i.e., a maximum of 4 grams daily for 10 days) presents any additional risk for these consumers compared to consumers without this condition. We considered the need for such a warning because we received a submission (Ref. 1) recognizing the potential risk of liver injury for consumers with Gilbert's syndrome who use acetaminophen. The submission argues that a warning regarding Gilbert's syndrome should not be required based on the available studies. We received this submission in response to our request in the 2006 proposed rule for comments and data on specific subsets of the population that may be at increased risk of liver injury when using the maximum daily dose of acetaminophen (71 FR 77314 at 77346).

Gilbert's syndrome is clinically characterized by serum bilirubin levels higher than normal and, in the cases where signs are apparent, causes yellow eyes and skin (jaundice). Gilbert's syndrome is harmless and requires no treatment (Ref. 43). Doctors diagnose patients as having the condition when examinations and tests do not reveal the existence of any other

condition causing the high bilirubin levels. The main cause of high levels of unconjugated bilirubin in these individuals is believed to be due to the reduced activity of the enzyme bilirubin-uridine diphosphate glucuronosyltransferase (UDP-GT), which is essential for the bilary excretion of bilirubin (Ref. 44). Acetaminophen is primarily eliminated by UDP-GT enzymes through a process called glucuronidation (Ref. 45). If the UDP-GT enzymes that metabolize acetaminophen do not function properly, then acetaminophen is metabolized through a metabolic pathway that produces the toxic metabolite NAPQI. Therefore, it has been suggested that individuals with Gilbert's syndrome may be at increased risk for acetaminophen-induced injury.

- We are not requiring a warning for consumers with Gilbert's syndrome because the available data do not demonstrate that consumers with Gilbert's syndrome are more likely to produce excess formation of NAPQI when using acetaminophen.

The submission that we received provided numerous articles and studies concerning Gilbert's syndrome (Ref. 1). Of these studies, the most meaningful in determining the risk of acetaminophen-induced liver injury are the three acetaminophen metabolism studies in individuals with Gilbert's syndrome (Refs. 46, 47, and 48). The studies compare the amount of the most abundant acetaminophen metabolites (conjugation products- glucorounides and sulphates) and/or the least abundant acetaminophen metabolites (oxidation products- cysteines and mercaptures) between the groups. The oxidation metabolites are formed through a process that generates NAPQI. Therefore, the metabolites are used as surrogates for NAPQI production.

The first study (Ref. 47) enrolled 32 control subjects and 18 Gilbert's syndrome subjects. The Gilbert's syndrome subjects were divided into two groups: (1) those who produced more conjugation acetaminophen metabolites than oxidation metabolites and (2) those who produced

more oxidation acetaminophen metabolites than conjugation metabolites. The second Gilbert's syndrome group represents subjects with abnormal acetaminophen metabolism because more conjugation acetaminophen metabolites than oxidation metabolites should be produced. One dose of acetaminophen (1.5 grams) was used, and urine was collected for 24 hours. Neither the control group nor the first Gilbert's syndrome group showed any statistically significant differences in the level of acetaminophen or any of its metabolites. The second Gilbert's syndrome group showed a statistically significant increase in oxidation metabolites and decrease in conjugation metabolites.

The second study was performed on six individuals with Gilbert's syndrome, and six control individuals (Ref. 46). Acetaminophen, 1.2 grams to 1.8 grams, was given. The conjugation metabolites were measured in plasma 2 hours after acetaminophen dosing, whereas the oxidation metabolites were measured in urine 24 hours after dosing. The conjugation metabolite levels were 31 percent lower in Gilbert's syndrome individuals compared to control individuals. The oxidation metabolites were 70 percent higher in Gilbert's syndrome individuals than controls. This study demonstrates statistically significant differences in both groups, and suggests lower glucuronidation and enhanced excretion of the oxidation metabolites in 24 hour urine samples of Gilbert's syndrome individuals. It is important to note that none of the Gilbert's syndrome individuals showed any elevation in liver function tests or any other sign of liver injury.

In the third study, 11 individuals with Gilbert's syndrome and 10 control subjects received 1 gram of acetaminophen orally (Ref. 48). Eight hours later urinary acetaminophen and its metabolites were measured by high performance liquid chromatography. The conjugation metabolites were 37.5 ± 4.7 percent versus 32.4 ± 2.4 percent in individuals with Gilbert's

syndrome and control group, respectively. The oxidation metabolites levels were 5.2 ± 1.8 percent versus 4.6 ± 1.2 percent in individuals with Gilbert's syndrome and control group, respectively. These results demonstrate that the relative amount of each metabolite was not significantly different between groups. Therefore, this study suggests that metabolism of acetaminophen is not altered in individuals with Gilbert's syndrome.

Results of the three metabolism studies are conflicting. The first two studies suggest decreased conjugation and increased oxidation of acetaminophen in individuals with Gilbert's syndrome. This finding suggests that greater amounts of the toxic metabolite may be produced by individuals with Gilbert's Syndrome. It is not clear, however, that this translates into an increased risk for developing acetaminophen-induced liver injury. However, the third study shows no difference in the conjugation and oxidation metabolite levels between individuals with or without Gilbert's syndrome. This finding suggests that these individuals may not produce different amounts of metabolites. We do not believe these three studies adequately demonstrate that individuals with Gilbert's syndrome are at higher risk of liver injury than individuals without Gilbert's syndrome when using up to 4 grams acetaminophen daily.

V. Labeling Required for OTC NSAIDs

A. Warnings

In response to the 2006 proposed rule, we received five submissions regarding warnings for OTC NSAIDs (Refs. 1, 2, 4, 5, and 49). While three submissions (Refs. 2, 4, and 49) agree with the proposed warnings, two submissions (Refs. 1 and 5) request the following revisions to the proposed warnings:

1. Revise the "Ask a doctor or pharmacist before use if you are" subheading in proposed 21 CFR 201.325(a)(2)(iii)(B) to read "Ask a doctor or pharmacist before use if you are taking."

2. Include "liver disease" in the kidney damage warning (proposed 201.325(a)(2)(iii)(b)). The first request was made because the proposed bulleted statements under the subheading all begin with "taking;" therefore, "taking" should be moved from the bulleted statements to the subheading. This revision would decrease the overall number of words for the warning. The second request concerns the warning that deals primarily with risk factors for kidney damage when using OTC NSAIDs. The submission (Ref. 1) includes data regarding the occurrence of kidney damage in patients with severe liver disease with ascites when using OTC NSAIDs.

We are not revising the proposed NSAID warnings in this document as suggested by the two submissions. Regarding the first request (Ref. 5), we cannot revise the warning subheading statement in proposed 21 CFR 201.325(a)(2)(iii)(B) because there are other proposed bulleted statements under this heading from the 2002 IAAA proposed rule (67 FR 54139 at 54150; 21 CFR 343.50(c)). One of the other proposed bulleted statements reads, "under a doctor's care for any serious condition." This bulleted statement would not make sense if "taking" is included in the warning subheading.

Regarding the second request, we are adding "liver cirrhosis" to the "Ask a doctor before use if you have" warning. The submission making this request submitted many different types of studies (Ref. 1). We believe the most clinically meaningful of the submitted studies are the seven prospective studies examining kidney function in patients with liver disease using NSAIDs. These studies enrolled a total of 112 patients with liver disease who took an NSAID. All of the patients had cirrhosis with ascites, a severe form of liver disease in which fluid collects in the abdomen. Fourteen of these patients also had functional kidney failure. The study end points examined kidney function by typical laboratory parameters, such as glomerular filtration rate, renal plasma flow, and serum creatinine levels.

Taken together, the study results suggest that kidney function decreases in these patients when they use an NSAID. For example, one study (Ref. 50) found that the decreases in three of the parameters were statistically significant ($p < 0.05$): glomerular filtration rate, renal plasma flow, and serum creatinine levels.

Patients with cirrhosis and ascites constitute a subset of the patients who have liver disease and represents a severe stage of liver disease. We are not aware of data demonstrating the patients with less severe forms of liver disease are at higher risk than consumers without liver disease. One of the submitted studies found only one of the seven kidney function parameters decreased significantly when comparing patients who had liver disease without ascites to patients who did not have liver disease (Ref. 51). In contrast, five of the seven kidney function parameters decreased significantly when comparing patients who had liver disease with ascites to patients who did not have liver disease. This result is consistent with what one would expect to see in patients with ascites, which causes loss of intravascular fluid due to accumulation of fluid in the abdominal cavity. The renin angiotensin system is activated, which results in renal vasoconstriction. The kidney produces vasodilating prostaglandins which help maintain renal function. In patients with cirrhosis and ascites, NSAIDs reduce the production of vasodilating prostaglandins, which could lead to a decline in renal function and development of renal failure (Refs. 52, 53, and 54).

In conclusion, we are including "liver cirrhosis" in the "ask a doctor" warnings instead of "liver disease" as requested by the submission because the results of the studies are consistent with an intravascular volume depleted condition caused by liver cirrhosis and ascites. It is important to note that these patients are typically under a high level of care by doctors because of the severity of the disease state. This is demonstrated by the submitted studies, in which 85 of

the 112 patients were hospitalized when they were enrolled in the studies. The medications that these patients receive are scrutinized by their health providers. Furthermore, we are not aware of data demonstrating that the majority of patients with less severe liver disease are at higher risk to develop a decrease in kidney function. Therefore, "liver disease" would be too vague, because it would also apply to patients with less severe forms of liver disease.

In addition to adding "liver cirrhosis" to the warnings, we are making other revisions to the warnings that we believe will improve the safe use of these products. We are revising the introductory sentences of the stomach bleeding warning to include "severe" before "stomach bleeding." We are making this modification because a submission (Ref, 1) argues that the term "severe" to qualify liver damage should be consistently applied to all OTC analgesics but was only proposed as part of the liver warning and was not proposed in the stomach bleeding warning (see Section IV.A.2. of this document). The same submission also argues that the term "severe" should not be used in either the liver warning or the stomach bleeding warning. However, we believe that the term is accurate and appropriate in both warnings because the drug-induced liver damage and bleeding can both potentially lead to death.

We are revising the introductory sentences of the stomach bleeding warning to remove the words "nonsteroidal anti-inflammatory drug" immediately before "(NSAID)." The term "NSAID" is defined under the "Active ingredient/Purpose" heading (21 CFR 201.326(a)(2)(ii)). It does not need to be defined a second time in the stomach bleeding warning. The introductory sentences of the stomach bleeding warning required in this document reads: "Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you." These sentences are followed by the bulleted statements identifying risk factors.

We are also removing warnings that are not part of the stomach bleeding warning but are related. There are five bulleted statements under the "Ask a doctor before use if you have" and "Ask a doctor or pharmacist before use if you have" headings that are redundant with bulleted statements under the stomach bleeding warning (proposed 21 CFR 201.325(a)(2)(iii)(B) and (C)):

- ulcers
- bleeding problems
- reached age 60 or older
- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug.

The stomach bleeding warning informs consumers of risk factors for stomach bleeding. These five bulleted statements instruct consumers to ask a doctor or pharmacist before using an NSAID if they have any of the stomach bleeding risk factors. Therefore, all of these proposed warnings are necessary. However, we believe the five bulleted statements can be simplified into one warning: "Ask a doctor before use if the stomach bleeding warning applies to you." This revised warning will provide consumers with the same information while taking much less labeling space. We should also note that this revision changes the heading so that we are also making minor revisions to the other bulleted statements under the "Ask a doctor before use if" heading.

All five bulleted statements are identical to the bulleted statements in the stomach bleeding warning except the statement about NSAID use. This statement specifies "prescription or nonprescription," which is not specified in the stomach bleeding warning. We believe this is important information that consumers should continue to be aware of. Therefore, we are revising

the fourth bulleted statement in the stomach bleeding warning to include this information: "take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)."

There are also two warnings related to stomach bleeding under the "Stop use and ask a doctor if" heading (proposed 21 CFR 201.325(a)(2)(iii)(D)):

● you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding

● stomach pain or upset gets worse

We continue to believe these warnings are important to the safe use of OTC NSAIDs. The stomach bleeding warning and the new warning "Ask a doctor before use if the stomach bleeding warning applies to you" provide information that consumers need to know before using an OTC NSAID. The warnings under the "Stop use and ask a doctor if" heading provide information that consumers need to know after they begin using an OTC NSAID. In this document, we are revising the warnings to make it clearer that both warnings relate to signs of stomach bleeding:

Stop use and ask a doctor if

● you experience any of the following signs of stomach bleeding:

  ● feel faint

  ● vomit blood

  ● have bloody or black stools

  ● have stomach pain that does not get better.

We believe this revision will allow consumers to more easily identify symptoms of stomach bleeding.

In addition to the revisions related to stomach bleeding, we are revising the warning

related to stomach pain and discomfort that can be caused by NSAID use (proposed 21 CFR 201.325(a)(2)(iii)(B)): "Ask a doctor before use if you have stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain." We continue to believe that OTC NSAIDs are more likely to lead to stomach pain and discomfort in consumers who have a history of stomach problem than those who do not (53 FR 46204 at 46220). Therefore, we are continuing to require this warning. But, we are revising it to make it more concise and easier to understand: "Ask a doctor before use if you have a history of stomach problems, such as heartburn." We believe all of the revisions that we are making to the OTC NSAID warnings in this document will better ensure safe use of these products.

B. Labeling Specific to Aspirin

In response to the 2006 proposed rule, we received one submission from a manufacturer of OTC aspirin products (Ref. 55). The submission requests the following for OTC aspirin products:

(1) Do not require the word "NSAID" on the PDP;

(2) Allow the indication statement "as directed by a doctor for prevention of heart attack and stroke"; and

(3) Do not require the cardiovascular risk warning proposed for all OTC NSAIDs.

In support of these requests, the submission cites the safe marketing history of aspirin and the unique pharmacological properties of aspirin that distinguish it from the other NSAIDs. The submission does not include any data to support these requests.

In this document, we are requiring the labeling proposed for aspirin in the 2006 proposed rule. The carton labeling covered by this final rule will include aspirin products. Regarding the submission's first request, we believe it is important to identify OTC aspirin products as being an

"NSAID." In the 2006 proposed rule, we proposed that the name of the NSAID ingredient (e.g., "aspirin") should be followed by the term "(NSAID)" as highlighted text on the PDP on all OTC NSAID products (71 FR 77314 at 77350). We proposed this labeling be required to help consumers identify NSAID-containing products and avoid adverse drug effects (e.g., stomach bleeding) caused by accidentally using multiple NSAID products at the same time. We believe that these adverse drug effects may occur regardless of whether an NSAID product contains aspirin or another NSAID. We are not aware of any data demonstrating that aspirin is significantly less likely to cause these adverse drug effects. For example, our AERS database reveals 279 cases of stomach bleeding associated with aspirin and other NSAIDs between 1998 and 2001, and the majority of reports involve aspirin (71 FR 77314 at 77325). Therefore, we continue to believe that the term "NSAID" prominently displayed on all OTC NSAID products, including aspirin, is important for the safe use of these products.

Regarding the submission's second request, we are not allowing OTC aspirin products to include the indication statement "as directed by a doctor for prevention of heart attack and stroke" in the "Uses" section of the "Drug Facts" label. OTC use of aspirin for cardiovascular uses is allowed under professional labeling for OTC aspirin products, although the indication statement is different than that included in the submission (21 CFR 343.80). In a 1993 proposed rule, we proposed the following warning be included on OTC aspirin labeling (58 FR 54224 at 54225): "IMPORTANT: See your doctor before taking this product for your heart or for other new uses of aspirin, because serious side effects could occur with self treatment." The intent of the recommended indication statement and proposed warning is to encourage consumers to seek a doctor's advice when using aspirin to prevent heart attack or stroke. We will consider these and other labeling options in a future FEDERAL REGISTER publication. In this document, we

are not addressing the submission's third request to exclude OTC aspirin products from including the cardiovascular risk warning (i.e., "long term continuous use may increase the risk of heart attack or stroke"). This warning was included on all OTC NSAID products except aspirin marketed under an NDA, as specified in the July 2005 letter sent to all OTC NSAID NDA holders (Ref. 6). We have not required that this warning be included on any aspirin-containing products. We have not proposed this warning for OTC NSAIDs marketed under the monograph. We will address this warning for OTC NSAIDs marketed under the monograph in a separate FEDERAL REGISTER notice because it was not included in the 2006 proposed rule (i.e., is not in proposed 21 CFR part 201).

VI. Analysis of Impacts

We have examined the impacts of this final 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 $100,000,000 or more (adjusted annually for inflation) in any one year." The

current threshold after adjustment for inflation is about $130 million, using the most current (2007) Implicit Price Deflator for the Gross Domestic Product.

We conclude that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This final rule is not a significant regulatory action as defined by the Executive Order and, therefore, is not subject to review under the Executive order. As discussed in this section, we have determined that this final 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 expenditure in any one year of $100 million or more, we are not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

We estimate that manufacturers and marketers of OTC acetaminophen and NSAID drug products would incur one-time compliance costs of $32 million in the first year to revise labeling to conform to this rule. The benefits of this final 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,[9] and $49 million to $147 million at a 3 percent discount rate. If we assume only a 1 percent reduction in the illnesses and deaths analyzed, the benefits of this rule outweigh the costs.

We note 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-

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

year period to reach a breakeven point. Social benefits would equal the costs of compliance if the rule prevents about 1 death each year (0.9 and 0.7 deaths over 10 years at a 7 percent and a 3 percent discount rate, respectively). Alternatively, if no deaths are avoided, the 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.

A. Need for the Rule

In 2002, an FDA Advisory Committee recommended changes to the labeling of OTC acetaminophen and NSAID drug products to better inform consumers about the active ingredients and possible side effects caused by improper use. Although we consider acetaminophen to be safe and effective when labeled and used correctly, using too much can lead to liver injury and death. Similarly, the use of NSAIDs can lead to stomach bleeding and kidney damage. 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 using 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, we find that there is sufficient incidence of liver injury 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 stomach adverse events, especially bleeding. The risk is higher for certain populations. Based on the evidence discussed in this document, we further find that NSAIDs increase the risk for stomach adverse events and that, without a new stomach bleeding warning in the labeling for NSAIDs, the products would no longer be considered generally recognized as safe and effective and not misbranded for OTC use.

The purpose of this final rule is to amend our OTC drug labeling regulations to include new warnings and other labeling requirements to advise consumers of potential risks and when to consult a doctor (see Table 1 in section I.B.2. of this document). We are also removing the alcohol warning in § 201.322 and incorporating new alcohol-related warnings and other labeling for all OTC acetaminophen and NSAID drug products. We are requiring certain warning information targeted to age-specific populations. In addition, we are requiring that the presence of acetaminophen or any NSAID would appear prominently on a product's principal display panel (PDP).

B. Impact of the Rule

We contracted Eastern Research Group, Inc. (ERG) to assess the costs and benefits of the

2006 proposed rule on which this final rule is based. The results of ERG's analysis apply to this final rule because there are only minor differences between the proposed rule and this final rule. We do not believe any of these differences will significantly changes the costs and benefits determined by ERG. 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. 56).

Manufacturers and marketers of OTC acetaminophen and NSAID drug products would incur one-time costs to revise affected product labeling to comply with this rule. 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.

To develop the original model, we 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 acetaminophen and NSAID drug product industry, the labeling revision process, the costs of modifying labeling, and the frequency of packaging reconfiguration changes.

The baseline for this action is in 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), we accounted for the total incremental costs to comply with requirements, including 6 point font size and related costs for increased

package size and longer labeling where applicable. We note 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 our requirements. The analysis assumes that one-half of the manufacturers of OTC acetaminophen and NSAID 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 acetaminophen and NSAID drug product stock keeping units (SKUs), split evenly among branded and private labels, according to an industry consultant.[10] We assume branded SKUs are distributed as follows 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 acetaminophen and NSAID drug products as follows: Acetaminophen, 45 percent; NSAIDs (except ibuprofen), 38 percent; ibuprofen, 15 percent; and combinations of acetaminophen and NSAIDs, 2 percent. 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

[10]Estimates of affected SKUs are 18,000 by FDA and 20,000 to 25,000 by industry consultant. This number of SKUs includes products marketed by manufacturers, repackers, relabelers, and distributors.

collect information on the distribution of types of OTC acetaminophen and NSAID drug product packaging. Roughly 80 percent of OTC acetaminophen and NSAID 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 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 peel back 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 2 presents the estimated total and annualized costs of compliance with the OTC acetaminophen and NSAID drug product final 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 (i.e., $15.2 million for 22,500 SKUs).

TABLE 2.—ESTIMATED TOTAL AND ANNUALIZED COSTS (AT 7 PERCENT DISCOUNT RATE) OF COMPLIANCE WITH THIS RULE

	Dollars (in millions)				
	Company Type	Acetaminophen	NSAIDs except Ibuprofen	Ibuprofen	Combinations of Acetaminophen and NSAIDs
Total Costs					
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					
Small Brand	1	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 final rule affects an estimated 258 manufacturers of OTC acetaminophen and NSAID drug products (200 of which are small businesses).

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, we believe 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 3 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 3.—ESTIMATED IMPACTS ON PHARMACEUTICAL PREPARATION MANUFACTURING FIRMS BY SIZE (NAICS 325412)

Firm Size (Number of Employees)	Average Receipts per Firm (Dollars in Millions)	Assumed Number of SKUs	SKUs per Firm	Total Firm Cost (Dollars in Thousands)[1]	Compliance Cost (% of Receipts)
<20	1.7	841	9	6.0	0.34%
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 calculate estimates includes both OTC and prescription drug manufacturers. However, no alternative revenue and employment size information for affected product lines is available. We conclude that this estimate of the impacts of this 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 our requirements. This rule does 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 this final rule; we are requiring removal of the existing alcohol warning in § 201.322.

D. Alternatives

We do not believe that there are any alternatives to the final rule that would adequately provide for the safe and effective use of OTC acetaminophen and NSAID drug products. Nonetheless, we considered but rejected the following alternatives: (1) Not adding the new information to OTC acetaminophen and NSAID drug product labeling, and (2) a longer implementation period. We do 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. We consider this final rule the least burdensome alternative that meets the public health objectives of this rule.

E. Benefits

Our final rule requirements are intended to enhance consumer awareness and knowledge of the active ingredient in OTC acetaminophen and NSAID drug products. These new warnings 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 requirements is to reduce the liver injury and stomach bleeding episodes that occur due to unintentional overdosing with these drugs. The requirements are also intended to reduce the incidence of adverse health outcomes among high-risk subpopulations consuming proper doses of OTC acetaminophen and NSAID drug products (e.g., people with liver disease or prone to stomach bleeding).

To estimate the benefits of this final rule, we developed baseline information on the frequency of hospitalizations, emergency room visits, and deaths related to unintentional overdosing with OTC acetaminophen and NSAID drug products. We used a value of $5 million to represent the premature loss of a statistical life in previous analyses (66 FR 6137). 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 (71 FR 77314 at 77341).

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 acetaminophen and NSAID drug products. Specifically, prominent display of the active ingredients on the PDP would alert consumers to the presence of the active ingredients in OTC acetaminophen and NSAID 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 acetaminophen and NSAID drug products more safely and lead to at least a modest reduction in unintentional overdosing.

Table 4 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 4. —SUMMARY OF ANNUAL MONETIZED BENEFITS OF ILLNESSES AVOIDED ASSOCIATED WITH THIS RULE (IN 2001 DOLLARS)

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 This Rule[2]	Total Annual Monetized Benefits of Illness Avoided (Dollars in Thousands)
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 kidney failure with hospitalization	$22,251	Not Estimated	$22,251	5	0.05-0.15	$1.1-$3.3
Acute kidney failure with dialysis	$22,251	Not Estimated	$22,251	0.7	0.007-0.021	$0.2-$0.5
Stomach bleeding	$14,653	$357	$15,010	61	0.6-1.8	
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 final rule would reduce annual adverse event cases by 1 to 3 percent (71 FR 77314 at 77344).

In addition to estimating the value of preventing adverse drug events that result in emergency department or hospitalization, we considered the annual number of deaths related to unintentional acetaminophen overdoses. We estimate that from 1996 to 1998, an annual average of 100 adult deaths were related to unintentional acetaminophen overdoses (71 FR 77314 at 77344). We assume this rule would reduce deaths by 1 to 3 percent annually. Applying a value of $5 million for each death prevented, we estimate the total benefits associated with preventing 1 to 3 deaths to be $5 to $15 million annually (in 2001 dollars).

If the required improved labeling and warnings reduced serious adverse events by 1 to 3 percent each year, the total monetized value of preventing illness and death 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 final 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 final rule, assuming a 1 percent reduction in current levels of adverse health outcomes associated with the use of OTC acetaminophen and NSAID drug products, will more than offset the costs of this rule. Table 5 summarizes the estimated benefits and costs of this final rule.

TABLE 5.—SUMMARY OF IMPACTS

Benefits/Costs	Dollars (in Millions)
Benefits:	
● Monetized 1 and 3 percent reduction in illnesses and deaths per year	$6–$17
● Present value over 10 years at 7 percent	$41–$126
● Present value over 10 years at 3 percent	$49-$147
Costs:	
● One-time label revision, first year	$33

Break-Even Analysis.

We note 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 break-even point (i.e., the cost of compliance/present value of avoiding one death each year for 10 years). This final rule would need to prevent about 1 death each year over 10 years [0.9 deaths ($32/$37.6 million at a 7 percent discount rate) and 0.7 deaths ($32/$43.9 million at a 3 percent discount rate)]. Alternatively, if no deaths are avoided, the final 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 deaths analyzed, the benefits of this final rule outweigh the costs. We find that this final rule will enhance public health and promote the safer use of OTC acetaminophen and NSAID drug products.

This economic analysis, together with other relevant sections of this document, serves as

our final regulatory flexibility analysis, as required under the Regulatory Flexibility Act. We did not receive any submissions regarding the economic analysis in the 2006 PR.

VII. Paperwork Reduction Act of 1995

We conclude that the labeling requirements 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 labeling statements are a "public disclosure 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)).

VIII. Environmental Impact

We have determined under 21 CFR 25.31(a) that this 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.

IX. Federalism

We have determined that the rule will 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 (the act) (21 U.S.C. 379r(a)) is an express preemption provision. Section 751r(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 requirement related to the regulation of nonprescription drug products. Section 751(b) through (e) of the act outlines the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.

This final rule will require important new organ-specific warnings and related labeling requirements for OTC IAAA drug products. The new labeling informs consumers about the risk of liver injury when using acetaminophen and the risk of stomach bleeding when using NSAIDs. Although this final rule would have a preemptive effect, in that it would preclude States from promulgating requirements related to these 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 US 861 (2000)).

We believe that the preemptive effect of the final rule would be consistent with Executive Order 13132. Section 4(e) of the Executive Order provides that "when an agency proposed 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."

In conclusion, we believe that we have complied with all of the applicable requirements under the Executive order and have determined that the preemptive effects of this rule are consistent with Executive Order 13132.

X. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) under Docket No. 1977N-0094L and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. C7.

2. Comment No. C3.

3. Comment No. EMC1.

4. Comment No. EREG4.

5. Comment No. C6.

6. Letter from Charles Ganley, FDA, to NSAID NDA Holders, July 2005.

7. Comment No. EC1.

8. Comment No. EC2.

9. Comment No. EREG1.

10. Comment No. C5.

11. Comment No. EC4.

12. Comment No. C8.

13. Bower, W. A. et al., "Population-Based Surveillance for Acute Liver Failure," 8th Ed., 102:2459-63, 2007.

14. Watkins, P. B. et al., "Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily: a Randomized Controlled Trial," Journal of the American Medical Association, 296:87-93, 2006.

15. Larson, A. M. et al., "Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study," Hepatology, 42:1364-1372, 2005.

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List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is 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, 360gg-360ss, 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 § 201.326(a)(1)(iii) and/or stomach bleeding warning set forth in § 201.326(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. Remove § 201.322.

4. Section 201.326 is added to subpart G to read as follows:

§ 201.326 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) Statement of identity. The statement of identity appears in accord with §§ 201.61 and 299.4 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:

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

(B) 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.

(ii) Active Ingredient and Purpose Headings. The information required under §§ 201.66(c)(2) and (c)(3) of this chapter must be included under these headings. The information under these headings, but not the headings, may appear highlighted.

(iii) For products labeled for adults only. 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, which is the maximum daily amount [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. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers.

(B) “Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”

(C) “Ask a doctor before use if you have liver disease”.

(D) "Ask a doctor or pharmacist before use if you are taking the blood thinning drug warfarin" except on the labeling of combination products that contain acetaminophen and NSAID(s).

(iv) <u>For products labeled only for children under 12 years of age</u>.

(A) <u>Warnings</u>. The labeling of the product states the following warnings under the heading “Warnings”:

(<u>1</u>) “Liver warning [heading in bold type]: This product contains acetaminophen. Severe liver damage may occur if your child takes [bullet] more than 5 doses in 24 hours, which

is the maximum daily amount [bullet] with other drugs containing acetaminophen". This "Liver warning" must be the first warning under the "Warnings" heading. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers.

(2) "Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist."

(3) "Ask a doctor before use if your child has liver disease".

(4) "Ask a doctor or pharmacist before use if your child is taking the blood thinning drug warfarin" except on the labeling of combination products that contain acetaminophen and NSAID(s).

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

(v) For products labeled for adults and children under 12 years of age. 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, which is the maximum daily amount [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." If there is an outer and immediate container of a retail package, this warning must appear on both

the outer and immediate containers.

(B) “Ask a doctor before use if the user has liver disease.”

(C) “Do not use with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.”

(D) "Ask a doctor or pharmacist before use if the user is taking the blood thinning drug warfarin" except on the labeling of combination products that contain acetaminophen and NSAID(s).

(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) Statement of identity. The statement of identity appears in accord with §§ 201.61 and 299.4 of this chapter. 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:

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

(B) 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. 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 accordance with this paragraph, and the name(s) of the other active ingredient(s)

in the product on the PDP. Only the word "(NSAID)" needs to appear highlighted or in bold type, and in a prominent print size, as described in this paragraph.

(ii) Active Ingredient and Purpose Headings. The information required under §§ 201.66(c)(2) and (c)(3) of this chapter must be included under these headings. 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." The information under these headings may appear highlighted. However, the headings "Active Ingredient" and "Purpose" may not appear highlighted.

(iii) For products labeled for adults only. 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 severe 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 prescription or nonprescription NSAIDs (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 paragraph (a)(1)(iii) of this section must appear before the "Stomach bleeding warning" in this paragraph. If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers.

(B) "Ask a doctor before use if [bullet] stomach bleeding warning applies to you [bullet] you have a history of stomach problems, such as heartburn [bullet] you have high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] you are taking a diuretic".

(C) "Stop use and ask a doctor if [bullet] you experience any of the following signs of stomach bleeding:" [add the following as second level of statements: "[bullet] feel faint [bullet] vomit blood [bullet] have bloody or black stools [bullet] have stomach pain that does not get better"].

(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) "Stomach bleeding warning [heading in bold type]: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause severe stomach bleeding. The chance is higher if your child [bullet] has had stomach ulcers or bleeding problems [bullet] takes a blood thinning (anticoagulant) or steroid drug [bullet] takes other drugs containing prescription or nonprescription NSAIDs (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). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers.

(2) "Ask a doctor before use if [bullet] stomach bleeding warning applies to your child [bullet] child has a history of stomach problems, such as heartburn [bullet] child has not been drinking fluids [bullet] child has lost a lot of fluid due to vomiting or diarrhea [bullet] child has high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] child is taking a

diuretic".

(3) "Stop use and ask a doctor if [bullet] child experiences any of the following signs of stomach bleeding:" [add the following as second level of statements: [bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better"].

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

(v) For products labeled for adults and children under 12 years of age. The labeling of the product states all of the warnings in paragraphs (a)(2)(iii)(A) through (a)(2)(iii)(C) 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 severe 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 prescription or nonprescription NSAIDs (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). If there is an outer and immediate container of a retail package, this warning must appear on both the outer and immediate containers.

(B) The labeling states "Ask a doctor before use if [bullet] stomach bleeding warning applies to user [bullet] user has history of stomach problems, such as heartburn [bullet] user has

high blood pressure, heart disease, liver cirrhosis, or kidney disease [bullet] user takes a diuretic [bullet] user has not been drinking fluids [bullet] user has lost a lot of fluid due to vomiting or diarrhea".

(C) The labeling states "Stop use and ask a doctor if [bullet] user experiences any of the following signs of stomach bleeding:" [add the following as second level of statements: [bullet] feels faint [bullet] vomits blood [bullet] has bloody or black stools [bullet] has stomach pain that does not get better"].

(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 must bear on its 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.

Dated: January 15, 2008.

Jeffrey Shuren,
Associate Commissioner for Policy and Planning.

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