Dated: October 15, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–28410 Filed 10–22–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 178

[Docket No. 96F–0164]

Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers; Technical Amendment

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; technical amendment.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations for the use of sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl)phosphate as a clarifying agent in high density polyethylene intended for use in contact with food. When the regulation was last amended, the agency inadvertently omitted the limitation on the use level for the additive. This document corrects that inadvertent omission.

EFFECTIVE DATE: October 23, 1998.

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Center for Food Safety and Applied Nutrition (HFS–215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3081.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 16, 1996 (61 FR 65942), FDA published a document amending the food additive regulations to provide for the expanded safe use of sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl)phosphate as a clarifying agent in high density polyethylene intended for use in contact with food. The limitation added by this document was inadvertently omitted from the December 16, 1996, final rule due to an administrative error. Limiting the use level of the additive to no more than 0.30 percent by weight of the olefin polymers is supported by the administrative record of the final rule. Accordingly, FDA is amending the regulation to accord with the record.

List of Subjects in 21 CFR Part 178

Food additives, Food packaging.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 178 is amended as follows:

PART 178—INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS

1. The authority citation for 21 CFR part 178 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 379e.

2. Section 178.3295 is amended in the table in the entry for ‘‘Sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl)phosphate’’ by revising entry ‘‘3.’’ under the heading ‘‘Limitations’’ to read as follows:

§ 178.3295 Clarifying agents for polymers.

* * * * *

Substances	Limitations
* * *	* * * *
Sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl)phosphate (CAS Reg. No. 85209–91–2)	For use only: * * * * * 3. As a clarifying agent at a level not exceeding 0.30 percent by weight of olefin polymers complying with § 177.1520(c) of this chapter, item 2.2, where the finished polymer contacts food only of types I, II, IV–B, VI–A, VI–B, and VII–B as identified in Table 1 of § 176.170(c) of this chapter, and limited to conditions of use B through H described in Table 2 of § 176.170(c) of this chapter, or foods of types III, IV–A, V, VI–C, and VII–A as identified in Table 1 of § 176.170(c) of this chapter and limited to conditions of use C through G described in Table 2 of § 176.170(c) of this chapter.

Dated: October 16, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–28409 Filed 10–22–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 77N–094W]

Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to require an alcohol warning for all over-the-counter (OTC) drug products, labeled for adult use, containing internal analgesic/antipyretic active ingredients. The required warning statements advise consumers with a history of heavy alcohol use to consult a physician for advice about the use of OTC internal analgesic/antipyretic drug products. FDA is issuing this final rule after considering comments on the agency's proposed regulation for OTC internal analgesic, antipyretic, and antirheumatic drug products; a proposed regulation to establish an alcohol warning; recommendations of its Nonprescription Drugs Advisory Committee (NDAC) and Arthritis Drugs Advisory Committee (ADAC); and new data and information that have come to the agency's attention. This final rule is part of the ongoing

review of OTC drug products conducted by FDA.

EFFECTIVE DATE: April 23, 1999.

FOR FURTHER INFORMATION CONTACT: Debbie L. Lumpkins, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2241.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 16, 1988 (53 FR 46204), FDA published a notice of proposed rulemaking, in the form of a tentative final monograph (TFM), that would establish conditions in part 343 (21 CFR part 343) under which OTC internal analgesic, antipyretic, and antirheumatic drug products are generally recognized as safe and effective and not misbranded. In the preamble to the proposed rule of this current rulemaking, the agency addressed concerns raised in the 1988 proceeding about the need for a warning on the increased risk of liver toxicity when acetaminophen is taken with substances or drugs that induce microsomal enzyme activity, i.e., alcohol, barbiturates, or prescription drugs for epilepsy (53 FR 46204 at 46217). The agency found that the available data did not provide a sufficient basis to require such a warning at that time. Interested persons were invited to submit new data or file written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal.

In response to the proposed rule, the agency received a number of comments containing new data addressing the need for an alcohol warning for acetaminophen. Copies of the comments received are on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

On June 29, 1993, NDAC met to consider the need for an alcohol warning for acetaminophen. NDAC concluded that heavy drinkers are at increased risk for developing liver toxicity when using acetaminophen and recommended that the labeling of OTC analgesic/antipyretic drug products containing this ingredient bear an alcohol warning. However, NDAC recommended that the agency not implement an alcohol warning for OTC analgesic/antipyretic drug products containing acetaminophen until it had a chance to consider data on the risk of alcohol use with other internal analgesic/antipyretic ingredients.

On September 8, 1993, NDAC and ADAC (the Committees) met jointly to evaluate the available data on the use of aspirin and other OTC analgesics by heavy alcohol users or abusers. The Committees concluded that the use of aspirin, ibuprofen, and naproxen sodium increases the risk of upper gastrointestinal (UGI) bleeding in heavy alcohol users or abusers. Concerning whether the data support an alcohol warning for OTC drug products containing these ingredients, the Committees voted 12 yes, 2 no for aspirin; 12 yes, 2 no for ibuprofen; and 12 yes, 1 no, and 1 abstention for naproxen sodium. The Committees further concluded that a recommendation on the need for an alcohol warning for OTC drug products containing other monograph salicylates (carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate) was outside their advisory scope.

In the **Federal Register** of November 14, 1997 (62 FR 61041), the agency published a proposed amendment of part 201 (21 CFR part 201) that would establish alcohol warnings for all OTC drug products labeled for adult use containing internal analgesic/antipyretic active ingredients. This warning would be required for all OTC internal analgesic/antipyretic drug products whether marketed under an OTC drug monograph or an approved new drug application (NDA).

In the proposal to amend part 201, the agency advised that any final rule based on the proposal will be effective 6 months after the date of publication in the **Federal Register**. Therefore, on or after April 23, 1999, any OTC drug product that is subject to this final rule, that contains nonmonograph labeling may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the effective date of the rule must be in compliance with the rule regardless of the date that the product was initially introduced or initially delivered for introduction into interstate commerce.

II. The Agency's Response to Comments

A. Comments on Specific Ingredients

1. Two comments argued that the agency's proposed requirement for an alcohol warning for OTC analgesic/antipyretic drug products containing aspirin is not based on sound scientific evidence. One comment asserted that it is necessary for FDA to demonstrate that a significant risk of gastrointestinal (GI) bleeding would result if heavy alcohol users were not specifically warned against the use of aspirin. Both comments suggested that the proposed requirement is contrary to agency statements in the TFM for OTC internal analgesic/antipyretic drug products that warning statements should be ''limited to those that are scientifically documented, clinically significant, and important for the safe and effective use of products by consumers'' (53 FR 46204 at 46213).

In support of this position, one comment included data that purport to show that heavy alcohol use: (1) Does not increase the risk of stomach bleeding (Refs. 1 through 4), (2) alcohol protects against GI problems (Refs. 5 and 6), and (3) GI bleeding in patients who reported prior aspirin and alcohol use is not more severe (Ref. 7). The comment also asserted that its evaluation of the adverse drug reaction data contained in FDA's Spontaneous Reporting System (SRS) failed to demonstrate a correlation between GI bleeding and heavy alcohol use, although the results of this evaluation were not included.

Another comment supporting the need for an alcohol warning for OTC analgesic/antipyretic drug products containing aspirin reviewed the data evaluated by the agency during the development of its proposal. To substantiate the need for an alcohol warning for aspirin, the comment also included data from a recently published study of the relationship between aspirin and nonsteroidal anti-inflammatory drug (NSAID) use and GI perforation (Ref. 8).

The agency continues to believe that warning statements should be limited to those that are scientifically based, clinically relevant, and important for the safe and effective use of these products by consumers. The agency disagrees with the comments asserting that the alcohol warning is not based on solid scientific evidence. An alcohol warning is needed for OTC analgesic/antipyretic drug products containing nonsteroidal anti-inflammatory ingredients, including aspirin. This warning is based on the data and information on the adverse GI effects of aspirin and other NSAID ingredients, the adverse GI effects of alcohol use, and the documented risk of combining them.

Although the previous comments pertain specifically to aspirin-containing OTC analgesic/antipyretic products, the agency's response will provide the scientific reasoning for applying the alcohol warning

requirement to the pharmacologic class of OTC analgesic/antipyretic drug products containing nonsteroidal anti-inflammatory ingredients, which include aspirin, nonaspirin salicylates, ibuprofen, ketoprofen, and naproxen sodium.

These OTC analgesic/antipyretic drug products contain NSAID ingredients, which belong to the carboxylic acid class. Aspirin and other salicylates are salicyclic acids; ibuprofen, ketoprofen, and naproxen sodium are derivatives of propionic acid. All of these ingredients share certain pharmacologic properties, including inhibitory effects on prostaglandin synthesis and platelet function. As with aspirin, propionic acid derivatives produce adverse GI side effects, alter platelet function, and can affect bleeding time (Refs. 9 through 14). Adverse GI effects are caused by aspirin and nonaspirin NSAID ingredients, which can irritate the mucosal epithelium (stomach lining) directly and/or can suppress prostaglandin synthesis. Prostaglandins normally help protect the stomach lining by promoting secretion of mucus and bicarbonate, repair of epithelial (lining) cells, immune cell function, and blood flow. Adverse bleeding effects can occur because NSAID's inhibit platelet aggregation.

Although there are data and information available concerning all of these ingredients, the largest body of data relied upon by the agency pertains to aspirin. Because these NSAID ingredients all share similar pharmacologic properties and can all cause adverse GI effects, including bleeding, it is reasonable for the agency to rely on the data pertaining to individual ingredients and to reason and apply these data to all of these NSAID ingredients. More specific comments concerning other ingredients will be addressed elsewhere in section II of this document.

Drug-related adverse effects can be evaluated through clinical data collected various ways, including randomized controlled trials, cohort studies, case-control studies, surveys, and spontaneous case reports. Prospective, randomized, blinded clinical trials require large patient enrollments to demonstrate a difference between groups when adverse events are infrequent, even if serious. Thus, most studies which examine the adverse GI effects of NSAID's are observational rather than experimental. Observational studies provide important information when investigating an association between a risk and a predisposing event. However, these studies may be subject to specific biases which should be considered. For example, case-control studies examine the prevalence of NSAID (and alcohol) exposure in patients who already have the outcome (GI events or bleeding) with a control population, which is matched for other factors. These studies may suffer from recall bias; that is, individuals in cases may be more likely than controls to remember that they took an NSAID (or alcohol). When reviewing these data from various studies, the agency has taken into account the limitations of each study method. Despite the limitations of individual studies, the data generated by each of these methods collectively provide a sound body of evidence from which it is scientifically reasonable to assess risk. Therefore, the agency believes that the collected body of scientific evidence supports the labeled warning.

As previously discussed in the notice of proposed rulemaking (62 FR 61041 at 61049), the adverse GI effects of aspirin are well known. Medical texts document adverse effects associated with the use of aspirin. These effects include, but are not limited to, gastritis, ulcerations, and colitis (Refs. 15 through 18). In addition, aspirin irreversibly interferes with normal platelet function for the life of the platelet, prolongs the bleeding time, and interferes with clotting whenever bleeding occurs (Ref. 13). Nonsalicylate NSAID ingredients reversibly inhibit platelet aggregation for as long as the drug is in the blood (Refs. 13 and 14). GI mucosal damage caused by aspirin has been widely acknowledged in the medical literature (Ref. 15 through 18), confirmed by endoscopic observational studies (Ref. 19), and taught through medical texts to students of medicine (Ref. 20).

In 1977, the Advisory Review Panel for OTC Analgesic and Antipyretic Drug Products (the Panel) first reviewed relevant data and concluded that aspirin causes adverse GI effects. The Panel concluded that the adverse effects of aspirin on the GI system range from relatively mild effects such as gastric distress (minor stomach pain, heartburn, or nausea), mucosal irritation and occult (not easily seen) bleeding, to less frequent but more serious effects such as mucosal erosion, ulceration, and life-threatening massive bleeding. The Panel further concluded that the acute use of aspirin may activate symptoms of both gastric and duodenal ulcer (42 FR 35346 at 35386 through 35397, July 8, 1977).

In addition to the Panel's conclusions, FDA also evaluated published literature, including studies which demonstrate adverse GI effects even with low-dose aspirin use (Refs. 21 and 22). The agency also reviewed data from controlled, prospective clinical trials on aspirin for cardiovascular and cerebrovascular uses and established that bleeding can occur with long-term aspirin use, even at low doses (62 FR 61041 at 61050).

Just as aspirin is well known to produce adverse GI effects, including bleeding, it is also well known that alcohol is a gastric toxin and that heavy alcohol use may cause a number of adverse GI effects, including bleeding. Routinely heavy alcohol use is associated with a number of medical conditions. These conditions include, but are not limited to, esophagitis, varices, acute gastritis, hemorrhagic lesions of the duodenal villi, and peptic ulcer disease (Refs. 23 through 28). Also, chronic heavy alcohol use can cause bleeding because of increased prothrombin time, decreased circulating platelets, and altered function of platelets (Ref. 13). Early (Ref. 23) and continuing (Refs. 24 through 26) study of the effects of alcohol on the stomach have been widely published in the scientific literature and alcoholic gastritis is a well-recognized cause of acute hemorrhagic gastritis (Ref. 29). These effects of heavy, chronic alcohol use on the GI system and bleeding parameters are explained in many standard medical textbooks (Refs. 25, 27 and 28).

The Panel recognized alcohol as a major factor that may produce acute gastric mucosal lesions, and thus increase the risk of bleeding from the use of aspirin (42 FR 35346 at 35479). Given these observations and the well established and recognized medical acceptance of GI and bleeding problems associated with the use of either aspirin or alcohol, the agency was concerned about the risks present for consumers who routinely and heavily drink alcohol and also use aspirin. This concern led to a review of relevant medical literature and studies (Refs. 8, 30, and 31), which confirmed the increased risk of adverse GI events, including bleeding, when alcohol use and aspirin use are combined.

Published studies which include randomized controlled clinical trials (Refs. 32 through 35), case-control studies (Refs. 8, 36 through 39a), cohort studies (Ref. 40), meta-analyses (Refs. 41 and 42), physician surveys (Ref. 31), and case reports (Ref. 43) have established an association between NSAID's, including aspirin, and adverse GI events, including bleeding. Because chronic alcohol use causes GI disease and bleeding, some studies simply exclude these patients from entry or analysis when assessing the risk of NSAID use on adverse GI outcomes (Ref.

44). However, some studies have examined both NSAID and alcohol use (Refs. 8, 30, 31, and 45) and assessed the risk of developing adverse GI events, including bleeding.

P. J. DeSchepper et al. (Ref. 45) measured fecal blood loss in 10 healthy males in a double-blind, parallel study and in 12 healthy subjects in a double-blind crossover study. Fecal blood loss was demonstrated with aspirin ingestion and concomitant ingestion of alcohol significantly increased (by three times) this blood loss.

D. Aarons et al. (Ref. 30) conducted a double blind prospective study of 27 healthy volunteers with initial normal baseline endoscopies who were given alcohol and either placebo, aspirin, or acetaminophen. Repeat endoscopy showed that alcohol and aspirin together caused significantly greater erythema (redness) due to irritation and hemorrhage in the stomach than alcohol alone.

The agency has reviewed adverse events reported to its SRS data base (Ref. 43). From 1993 to 1995, 37 case reports were submitted for serious UGI bleeding, 36 involving hospitalizations and 1 death. Most bleeds were documented by endoscopy. In these reports, ibuprofen was listed as the suspect drug in patients who reported chronic alcohol use (nearly 80 percent reported alcoholism or more than two drinks/day). Of important note, concomitant use of salicylates, primarily aspirin, was reported in almost 50 percent of these cases, thus associating both ibuprofen and/or salicylates with these reports of bleeding. From 1994 to 1996, five case reports were submitted for serious UGI bleeding with naproxen sodium listed as the suspect drug in patients who reported daily (or binge) alcohol ingestion. Two of these reports also listed salicylate use and two reports listed concomitant ibuprofen use. From 1993 to 1996, 10 case reports were submitted for serious UGI bleeding with aspirin listed as the suspect drug in patients who also reported alcohol ingestion (more than 2 drinks/day or unspecified). All 10 cases were hospitalized. Cases of concomitant NSAID ingredient use were excluded. Thus, the agency's SRS data base provides additional serious adverse events documenting the association between NSAID ingredient use and UGI bleeding in persons with a history of chronic alcohol use.

In a prospective community clinical case study, Lee et al. (Ref. 46) endoscoped 400 consecutive patients hospitalized for UGI hemorrhage to identify factors which predispose patients who bleed from hemorrhagic erosive gastritis. Of the 74 patients with stomach bleeding, salicylate use (31 percent), alcohol use, usually chronic (27 percent), or both (16 percent) were reported. There was no case-matched control and relative risk was not assessed. However, this study demonstrates that patients who have experienced hemorrhagic erosive gastritis (stomach bleeding) commonly report having used alcohol and/or salicylates.

Peura et al. (Ref. 31) surveyed American College of Gastroenterology physicians to assess demographics, management strategies, and outcomes for 1,235 patients who were diagnosed with GI bleeding. OTC doses of NSAID's were associated with a three-fold increased risk for developing GI bleeding and alcohol use increased this risk to four-fold.

Lanas et al. (Ref. 8) conducted a single-center, prospective, case-controlled study, which examined the relationship between NSAID use, including aspirin, and GI perforation. Detailed clinical histories and laboratory tests were obtained in 76 hospital admitted patients with surgically documented GI perforations and in 152 matched case controls. Histories of NSAID use were confirmed by measuring platelet cyclo-oxygenase activity. In the study cohort, 67 percent of the patients used aspirin (90 percent of these were over-the-counter formulations). The calculated odds ratio (OR) for GI perforation in patients who had used an NSAID within a week prior to hospitalization was 6.64 (95 percent confidence interval: 3.6–12.2; $p < 0.0001$) as compared to those who had not. Other independent risk factors for perforation included smoking (OR: 3.88; 95 percent CI: 2.15–7.0; $p<0.0001$), alcohol ingestion (OR: 3.25; 95 percent CI: 1.81–5.82; $p<0.0001$), and peptic ulcer disease (OR: 3.29; 95 percent CI: 1.74–6.21; $p<0.0005$). The combination of NSAID's, smoking, and alcohol increased the risk of GI perforation (OR: 10.69; 95 percent CI: 3.60–29.87). Because the study was conducted in Spain, a small number of patients in both cohorts reported use of NSAID's which are not available in the United States. However, the study conclusions remain valid for the NSAID class and, importantly, for nonprescription aspirin.

Although acute ingestion of aspirin and alcohol causes gastric hemorrhage (Ref. 30) in previously normal gastric mucosa, the increased bleeding risk from NSAID's in chronic heavy alcohol users can be further compounded by coexisting problems such as prolonged prothrombin time due to liver disease, decreased number of circulating platelets, and pre-existing GI disease (e.g., esophageal varices, ulcers, or alcoholic gastritis) (Ref. 13). Alcohol also potentiates the prolongation of bleeding time produced by aspirin and nonaspirin NSAID's, including ibuprofen (Ref. 14). A retrospective cohort study, using a Medicaid data base, was designed to determine the risk and cost of adverse GI effects associated with NSAID use (Ref. 47). Logistic regression analysis showed NSAID use was significantly associated with each defined GI side effect (i.e., ulcers, gastritis, bleeding) ($p<.001$) and alcohol-related diagnoses were a significant independent predictor of increased risk ($p<.05$) for GI bleeding and hemorrhagic gastritis. Therefore, co-existing GI and bleeding problems in chronic heavy alcohol users may pre-dispose to the increased bleeding risk from NSAID ingredients.

The data and studies presented provide sound and convincing evidence to support the conclusion that consumers are at increased risk of adverse GI effects when using OTC analgesic/antipyretic products, including aspirin, in combination with routine heavy alcohol use (Refs. 8 and 31). While the data and studies show that there is an increased risk to consumers who combine these drug products with routine heavy alcohol use, the agency acknowledges that the data differ as to the exact magnitude of this increased risk.

The agency again convened expert advisors in 1993 (Refs. 48 to 50) in three separate advisory committee meetings with NDAC and ADAC, to discuss the question of whether OTC analgesic/antipyretic products containing aspirin should bear an alcohol warning. The advisory committee experts concluded that aspirin increases the risk of UGI bleeding in heavy alcohol users or abusers and overwhelmingly concluded that the data support an alcohol warning for aspirin. A complete discussion of this conclusion can be found in the proposed rulemaking (62 FR 61043 through 61044).

The agency has reviewed the data and information submitted with the comments, which both oppose and support a requirement for an alcohol warning on OTC analgesic/antipyretic drug products containing NSAID ingredients, including aspirin. The agency's analysis of these data follows.

Holvoet et al. (Ref. 1) was reviewed by the Committees which heavily criticized the study design and did not use it as a basis for their recommendation (Ref. 48). Coggon, Langman, and Spiegelhelter (Ref. 2) was a case-control

study in patients with GI bleeding which reported an increased risk (OR of 3.7, 95 percent CI: 2.2–6.4) for patients who had recently used aspirin; but this study did not detect an added risk associated with alcohol use. However, the study groups were not balanced for alcohol-use history ($p<0.02$), compromising the ability of the study to determine the additional risk, if any, in heavy alcohol users. Bartle, Gupta, and Lazor (Ref. 3) failed to detect an increased risk of acute UGI bleeding with weekly alcohol ingestion of 280 milliliters. The investigators noted, and the agency concurs, that more patients would be required to assess whether or not an association exists. Although Schubert et al. (Ref. 6) reported a decreased risk of duodenal ulcer disease with alcohol use, the study lacked a matched case-control comparator arm and failed to quantify alcohol ingestion and other co-factors which may be associated with risks for developing ulcer disease.

Likewise, the Cohen et al. (Ref. 5) study submitted to demonstrate that alcohol is protective against GI bleeding caused by aspirin is not relevant because this study excluded patients without existing GI disease and those who drank more than two alcoholic drinks per day. Thus, the study excluded the very target population required to answer the question addressed by the agency, namely, individuals who consume three or more alcoholic drinks every day and/or have concomitant alcohol associated GI disease. The investigators concluded, and the agency concurs, that it is impossible to determine from this study that alcohol protects patients who take aspirin.

Jensen et al. (Ref. 7) reported that alcohol and aspirin use prior to hospital admission for the treatment of UGI bleeding was not associated with certain surrogate variables which were used to estimate the severity of GI bleeding. All patients were selected because they required medical treatment for severe UGI hemorrhage, and information was collected regarding alcohol and aspirin use. However, the study was not analyzed to evaluate whether reported concomitant aspirin and alcohol use is associated with a higher risk for developing UGI bleeding. Therefore, this study did not address the basic question before the agency, namely, whether there is an increased risk of stomach bleeding in patients who consumed both alcohol and aspirin.

Soll (Ref. 4) is a review article on peptic ulcer disease presented by an expert gastroenterologist. The article reviews the scientific literature and concludes that NSAID's, including aspirin, produce topical irritative effects on the mucosa as well as ulcerations as a consequence of a systemic effect. Therefore, NSAID's, which are rectally delivered or enteric coated may still cause adverse GI effects. Similar reviews have been published elsewhere (Refs. 51 and 52). Thus, while the article was submitted in opposition to a warning, the information in the article supports the scientific rationale for a warning.

A case-controlled study was also submitted which supports the need for an alcohol warning on OTC analgesic/antipyretic drugs containing NSAID ingredients (Ref. 8). This study has been previously summarized earlier in this response to comment 1 of section II.A of this document.

Given the data available at this time, the agency cannot precisely quantify the increased risk of combining routine heavy alcohol use and these OTC drug products. In order to require an alcohol warning, however, it is not necessary that the agency be able to demonstrate precisely how much the risk is increased. The available data demonstrate clearly that the risk to consumers of combining heavy routine alcohol use with these drug products is greater than the risk of using either alcohol or these drug products alone. These data are sufficient to establish the need for an alcohol warning on these OTC products. In light of the clearly demonstrated increased risk to consumers, the agency is requiring an alcohol warning about the risk of stomach bleeding on aspirin and other NSAID-containing OTC drug products.

In summary, OTC analgesic/antipyretic drug products, including aspirin, are known to cause adverse GI effects, including bleeding. Chronic, heavy alcohol use is also associated with adverse GI effects, including bleeding. Based on the agency's review of a large body of scientific information and in concurrence with expert advisors, FDA has determined that routine, heavy (three or more alcoholic drinks every day) alcohol use in combination with use of OTC analgesic/antipyretic drug products containing NSAID ingredients increases the risk of adverse GI events, including stomach bleeding. The agency believes that the most appropriate public health response to this information concerning risk is to warn consumers who drink three or more alcoholic drinks every day to consult their doctor about their use of these OTC drug products. This conclusion is scientifically based, clinically relevant, and important for the safe and effective use by consumers of OTC analgesic/antipyretic drug products containing NSAID ingredients.

2. One comment argued that FDA's conduct of this rulemaking violates the Administrative Procedure Act (APA). The comment stated that the APA requires that a notice of proposed rulemaking include ''either the terms or substance of the proposed rule or a description of the subjects and issues involved'' (5 U.S.C. 553(b)). The comment maintained that the agency's proposal fails to adequately describe the basis for the requirement for an alcohol warning for OTC drug products containing aspirin. The comment asserted that FDA denied interested parties adequate notice of the action by failing to expressly state its reliance on a ''switch rationale,'' i.e, the concern that an alcohol warning on one analgesic would cause inappropriate ''switching'' to other OTC analgesic/antipyretic drug products. The comment further argued that the agency's failure to obtain the raw data from unpublished epidemiological studies presented to the Committees that made recommendations also effectively denied interested parties the opportunity to comment fully.

Another comment suggested that the ''switch rationale'' is flawed. The comment asserted that there is no evidence that heavy alcohol users would be persuaded to change their analgesic use based on an alcohol warning. One comment noted that after several years of voluntary alcohol warnings on products other than aspirin, market tracking data for aspirin sales for the years of 1994 to 1997 have demonstrated that ''switching'' does not occur.

The intent of the warning is to advise consumers with a history of heavy alcohol use (three or more alcoholic drinks every day) to consult a physician for advice about the use of all OTC analgesic/antipyretic products and to advise that there is a specific risk associated with use of these products. The agency agrees that it is important not to encourage consumers who consume three or more alcoholic drinks every day to begin to use another OTC analgesic/antipyretic drug product before consulting their physician. In comment 1 of section II.A. of this document, the agency describes the scientific basis for requiring an alcohol warning for OTC analgesic/antipyretic drug products containing NSAID's, including aspirin. This rationale is also present in the agency's proposal (62 FR 61041 at 61049).

As discussed in the proposed rule (62 FR 61041 at 61049), the agency agreed with the assessment of the Advisory

Committees who made recommendations on the unpublished data presented before the committees. Raw data were not evaluated by the agency, do not serve as the agency's basis for this final rule, and are not required to be placed in the administrative record. The agency disagrees that interested parties were given insufficient opportunity to comment fully on the data. Comments on the presentations to the Committees as well as the Committees' recommendations (Ref. 53) were included in the administrative record. Further, the comments' criticisms of the unpublished data presented in September 1993 were sent to the members of the Committees for their specific comment. Of the responses received (Ref. 54), none stated that the comments' criticisms changed their recommendation. The agency has included in the administrative record the relevant data and information that were considered and relied upon regarding the warning statement requirements of the final rule. Therefore, the agency considers the requirements of the APA to be fully satisfied.

3. Three comments asserted that the imposition of an alcohol warning on aspirin could result in a significant adverse impact on public health. The comments said that placing an unnecessary ''stomach bleeding'' warning on aspirin may cause consumers taking it for its cardiovascular and cerebrovascular benefits to avoid using aspirin. The comments suggested that poor compliance with cardiovascular and cerebrovascular aspirin regimens could be detrimental to consumers at risk for these events. One comment noted that consumers on a long-term professional use regimen would be under a doctor's supervision and would presumably be warned about the risks of aspirin use and would be monitored for GI injury. Another comment maintained that the low doses used in long-term professional use aspirin regimens have not been associated with significant GI problems.

In its proposal, the agency evaluated the published literature on aspirin for cardiovascular and cerebrovascular uses and determined that bleeding can occur with long-term aspirin use, even at low aspirin doses. The proposal also discussed the use of alcohol in patients with cardiovascular problems and noted the recommendations of the American Heart Association (AHA) that consumers with these conditions should not consume alcohol heavily (62 FR 61041 at 61050). The proposal further reviewed the increased risk of cardiovascular diseases, such as heart muscle disease, hypertension, disturbances in heart rhythm, and stroke from heavy alcohol use. The intended purpose of this warning is to promote a dialogue between physicians and individuals who consume three or more drinks every day. The agency believes that this dialogue should extend to consumers on long-term aspirin regimens who may be adding to their risk of adverse vascular events by their alcohol consumption. Therefore, the agency concludes that an alcohol warning on OTC analgesic/antipyretic drug products containing aspirin will provide important advice to consumers on long-term, low-dose vascular regimens.

4. Two comments argued that to the limited extent that consumers are at risk from aspirin use, they are already alerted to this risk by warnings included in the TFM for OTC internal analgesic/antipyretic drug products (53 FR 46204). Specifically, the comments asserted that the proposed warning in § 343.50(c)(1)(v)(B) that states: ''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,'' is sufficient to warn consumers with stomach problems, whether due to heavy alcohol use or another condition, about the risk of aspirin.

The warning in § 343.50(c)(1)(v)(B) is intended to warn consumers with diagnosed stomach ulcer or symptoms of stomach distress to avoid the use of aspirin, unless directed to do so by a doctor. However, as noted in the agency's proposal, acute hemorrhagic gastritis accounts for 25 percent of major bleeding in heavy, chronic alcohol users and this condition may be asymptomatic (62 FR 61041 at 61049). For this reason, the agency finds that the currently proposed stomach distress warning does not adequately inform individuals who consume three or more alcoholic drinks every day of their risk.

5. Two comments stated the belief that the agency's proposed rulemaking did not evaluate the totality of the data for nonprescription ibuprofen. One comment argued that ibuprofen, even at prescription doses, has excellent GI tolerability. In support of its position, the comment cited data from a variety of different studies (Ref. 55) assessing the relative GI tolerability of prescription and OTC ibuprofen. The comments continued that the proposed rule does not acknowledge data demonstrating the excellent GI tolerabililty of ibuprofen, even when taken by individuals who regularly consume alcohol. Cited by the comment were: (1) The results of an endoscopic study of the effects of alcohol administration on the GI tolerability of 2,400 milligrams (mg) ibuprofen (twice the maximum daily OTC dose)/day (d) in healthy subjects (Ref. 56), (2) epidemiological studies previously evaluated by the agency (Refs. 57, 58, and 59) , and (3) an assessment of adverse reaction reports for OTC analgesic/antipyretic drug products containing ibuprofen (both prescription and OTC) contained in the agency's SRS data base for 1974 to 1993.

Another comment noted that while OTC drug products containing ketoprofen and naproxen sodium have been required to include an alcohol warning in their label, there are no clinical or meaningful epidemiological data to support the need for a warning on these products. Based on this lack of data, the comment maintained that an alcohol warning should not be required for any of the currently approved OTC NSAID's. To support its position, the comment cited the lack of reports of injury from the use of these products with alcohol and few reports of GI bleeding when these products are used as directed.

The agency concludes that an alcohol warning is needed for OTC analgesic/antipyretic drug products containing ibuprofen. Endoscopic data (Ref. 56) evaluating the GI tolerability in healthy subjects of prescription doses of ibuprofen (2,400 mg/d for 1 day) with 100-proof vodka are not adequate because the study did not assess the safety of ibuprofen use in individuals who consume three or more alcoholic drinks every day. Carson et al. (Ref. 59) reported that subjects with an alcohol-related diagnosis who took prescription ibuprofen had no material increase in bleeding. However, the Committees' evaluated the study by Carson and concluded that the population studied may not be generalizable (Ref. 48). The agency evaluated and discussed other studies (Refs. 57 and 58), which were not convincing as discussed in the proposed rule (62 FR 61041 at 61050).

Data concerning the relative GI tolerability of OTC ibuprofen are not sufficient to support the safety of ibuprofen in heavy alcohol users. Data from case-control studies which looked at the association between NSAID use and GI bleeding by Griffin et al. (Ref. 60), Savage et al. (Ref. 39), and Garcia Rodriguez and Jick (Ref. 61) were presented and publicly discussed at the October 11 and 12, 1995, Arthritis Advisory Committee Meeting (Ref. 62). All three of these studies found the use

of ibuprofen to be associated with a dose-dependent increase in risk for GI bleeding. The study by Somerville et al. (Ref. 38), which also looked at this issue, adds nothing to the discussion. Bradley et al. (Ref. 63) compared the effectiveness of low-dose ibuprofen (1,200 mg/d) to high-dose ibuprofen (2,400 mg/d) and high-dose acetaminophen (4,000 mg/d) in patients with osteoarthritis. This study confirmed the dose-dependent increase in GI symptoms associated with ibuprofen use (1,200 mg/d: 7/62, 11.3 percent; versus 2,400 mg/d: 14/61, 23.0 percent). None of these studies looked at the associated risks for gastrotoxicity and ibuprofen in individuals who consume three or more alcoholic drinks every day. DeArmond et al. (Ref. 64) is an abstract of safety data generated from 48 clinical trials evaluating OTC naproxen sodium versus ibuprofen and acetaminophen.

As previously discussed, study results displaying comparative risks among these analgesic products are difficult to interpret. However, because adverse GI effects, including bleeding, occur with all NSAID ingredients covered by this final rule, the warning is needed for all of these ingredients.

In conclusion, as previously discussed in comment 1 of section II.A. of this document, based on the similar pharmacologic properties of the nonaspirin NSAID ingredients available OTC as antipyretic/ analgesic drug products, the available scientific data for NSAID ingredients, alcohol, and the combination of nonaspirin NSAID's and alcohol, the agency concludes that an alcohol warning is needed for the safe and effective use of OTC drug products containing ibuprofen, ketoprofen, or naproxen sodium.

6. Several comments objected to the agency's requirement for an alcohol warning on OTC drug products containing carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate. These objections were based on the lack of data supporting the risk of the use of these products by individuals with a history of heavy alcohol use. The comments did not include data.

The agency notes that carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate were recognized by the Panel as having similar adverse effects on the GI tract as aspirin (42 FR 35346 at 35417 through 35422). Similar to aspirin, these adverse effects include gastric ulcer, exacerbation of peptic ulcer symptoms (heartburn and dyspepsia), GI hemorrhage and erosive gastritis (Ref. 65). These adverse effects can occur even at low doses. Based on the recognized individual GI toxicities of carbaspirin calcium, choline salicylate, magnesium salicylate, sodium salicylate, and alcohol as well as the Panel's recommendation that these OTC analgesic/antipyretic drug products bear similar labeling, including a warning against use of these OTC products in the presence of stomach distress, the agency concludes that an alcohol warning is necessary for the safe and effective use of OTC drug products containing these ingredients.

B. Comments on Labeling

7. Several comments objected to the inclusion of trade names and brand names in the proposed warning, because it would be confusing to consumers and would use up valuable label space. Two comments suggested using the name of the analgesic/antipyretic ingredient. Two comments suggested using the term ''this product,'' ''the product,'' or ''product'' in place of the trade name or brand name so that the warning would be generic for all OTC analgesic drug products. One comment suggested that even these terms (''this product,'' etc.) are superfluous and unnecessary. A comment contended that for cough/cold and analgesic combination drug products, the trade name could confuse consumers because only the analgesic ingredients pertains to the alcohol warning. Thus, consumers may infer that the warning was directed at each of the ingredients in a combination drug product.

The agency agrees that clear labeling is necessary. Inclusion of the name of the ingredient helps educate and alert the consumer by making the warning more precise. The agency also believes that the name of the specific analgesic/ antipyretic active ingredient would generally be more informative than the term ''this product'' or other similar terms. Therefore, the agency is revising the warning to include the analgesic/ antipyretic ingredient name instead of the brand name.

8. A number of comments were in disagreement as to the relative importance of the warnings for acetaminophen, aspirin, and other NSAID's. A number of comments said the established risks of acetaminophen use by heavy alcohol users far outweigh the risks of aspirin use by the same consumers. One comment submitted data from a comparative risk analysis of aspirin and acetaminophen (Ref. 66). Based on this analysis, the comment maintained that the number of expected deaths from acetaminophen toxicity when used for the short-term treatment of fever and pain is 12 times higher than that expected with aspirin.

Several comments complained that despite the much greater risk for acetaminophen, the proposed alcohol warning conveys the impression that for heavy alcohol users, the hazards of acetaminophen use and aspirin (or NSAID) use is essentially the same. Thus, consumers may be led to believe that they face a comparable risk with either analgesic. The comments said the proposed warning minimizes the essential messages. In support of this position, the comment included the results of a labeling comprehension study (Ref. 67) that it maintained demonstrated that consumers interpreted the warnings as conveying equivalent risks.

The agency has reviewed the analysis submitted by one comment (Ref. 66). There were numerous flaws in the baseline assumptions, some of which were noted by the analysis. The authors assumed that the maximum recommended daily dose of aspirin is 2,600 mg, but the maximum daily dose in OTC aspirin labeling is 4,000 mg. For comparative purposes, alcohol consumption should have been defined in terms of absolute alcohol. Deaths for GI bleeding and hepatotoxicity were based on articles from the literature rather than actual death rates in the United States attributed to either of these conditions. The authors summarized the data from case reports of hepatotoxicity due to ''therapeutic misadventure'' with acetaminophen to estimate the rate of hepatotoxicity associated with the drug. Cases of hepatotoxicity requiring transplantation were discounted in the analysis. It was assumed that the risk of GI bleeding with aspirin use starts at doses of 1,500 mg/d and the risk of hepatotoxicity with acetaminophen starts at about 4,000 mg/d. These data do not support an alcohol warning with comparative rates of risk.

The agency has also reviewed the labeling comprehension study (Ref. 67) and has determined that this study did not assess the risk communication of either warning. In the study, the warnings were not presented in context, as a consumer would be seeing them. Subjects were not allowed to perform comparative assessments of the two labels. In addition, the phrasing of three of the four agree/disagree statements made ''agree'' responses more likely. Finally, the results were not framed in terms of alcohol use, a key element in the relevant population of consumers. However, the study did reveal how few consumers were aware of these potential toxicities associated with aspirin or acetaminophen.

Although the risk of GI bleeding with aspirin is dose dependent, it can occur at any dose, depending on other comorbidity factors (Ref. 68). In addition to dosage, hepatotoxicity due to acetaminophen use is also dependent on factors such as liver glutathione stores, nutritional state, age, and in some cases, chronicity of usage. Thus, the agency concludes that the relative degree of risk between aspirin use and acetaminophen use can not be drawn from this analysis.

Finally, the agency believes there is some degree of risk for all OTC analgesic/antipyretic drug products in subjects that are chronic, heavy alcohol users. This risk is greater than for consumers of these products who are not chronic, heavy alcohol users. However, the degree of risk cannot be precisely calculated for the ''at risk'' population because different risk assessments vary from study to study and may increase with comorbid factors (Refs. 8 and 31) (62 FR 61041 at 61047). Nevertheless, it is likely that the degree of risk is not exactly the same for any two of these drug products or for any two individuals who consume three or more alcoholic drinks every day. The purpose of the alcohol warning in this final rule is to alert heavy alcohol users that serious, specific adverse events can occur with concomitant use of OTC drug products containing analgesic/antipyretic ingredients and to seek advice from their doctor in order to prevent serious adverse events whenever possible.

9. Several comments stated that the proposed alcohol warning for acetaminophen does not describe the severity of potential liver damage. One comment said the problem is not liver damage, but a significant risk of dying. A second comment said the term ''liver damage'' is vague and recommended that the warning include the phrase ''acute liver failure'' or ''sudden liver failure,'' or the term ''severe liver damage.''

In the majority of case reports the agency evaluated, acetaminophen-induced liver damage in heavy alcohol users did not result in liver failure or death. Therefore, the agency concludes that the statement ''Acetaminophen may increase your risk of liver damage'' provides an accurate description to the consumer.

10. One comment argued that the proposed three-drink threshold is not appropriate for the acetaminophen warning because it is far below what is reported in the cases cited by the agency. Therefore, the comment recommended that language be added to the warning to accurately describe the chronic heavy alcohol user. However, suggested language was not provided. One comment said that stating a specific number of drinks (''3 or more alcoholic beverages daily'') would be better than the general term ''excessive,'' because the later is very subjective and each person could define it differently. Another comment suggested that the warning does not adequately protect women. The comment based its contention on the U.S. Departments of Agriculture (USDA) and the Department of Health and Human Services (DHHS) guidelines that recommend only one drink per day for women (two for men) and evidence (Refs. 69 and 70) it believes demonstrates that women are more susceptible to the hepatic effects of alcohol. The comment suggested that the warning should be gender specific or should be changed to ''2 or more drinks a day'' in order to provide adequate protection for women.

The agency acknowledges that the level of alcohol consumption included in the proposed warning was intended as a general guideline to help consumers quantify their level of alcohol consumption (62 FR 61041 at 61052). This threshold is based on the recommendations from the dietary guidelines set by the USDA and DHHS and the standard set by the AHA. The agency notes that while the dietary guidelines for alcohol consumption set by USDA and DHHS differentiate between men and women, the standard set by AHA does not (62 FR 61041 at 61052).

The agency agrees with the comment that suggested a specific number of drinks is better than using the term ''excessive'' as a reference point for consulting a physician because it is more meaningful to many individuals as a specific number. The warning is intended to aid consumers in characterizing heavy alcohol consumption, in view of the inherent variability of individuals in their susceptibility to the toxic effects of both alcohol and OTC analgesic/antipyretic drug products.

11. One comment suggested using the word ''drinks'' instead of ''beverages'' in the proposed warning which states: ''If you drink 3 or more alcoholic beverages daily * * *.'' The comment said ''drinks'' is better understood by consumers, and noted that the agency based its analysis of alcohol consumption on the Dietary Guidelines for Americans, which defines ''drink.'' The comment said number of ''beverages'' could be perceived as the number of different kinds of drinks. For instance, a person could perceive four glasses of wine and four beers as two beverages. Another comment suggested using the term ''every day'' rather than ''daily'' in the warning because ''daily'' is often misunderstood to mean a single day, whereas ''every day'' is clearer in communicating a repetitive pattern of drinking behavior.

The agency agrees with the comments that the terms ''drinks'' and ''every day'' would better convey the intended message to consumers and has revised the warning to state: ''If you consume 3 or more alcoholic drinks every day * * *.''

12. One comment suggested that organ-specific warnings may be more appropriate for professionals than for consumers. The comment questioned whether the proposed warning would leave consumers puzzled as to which product to choose, one that causes liver damage or one that causes stomach bleeding. Thus an organ-specific warning may discourage consumers from consulting their physician, believing they can rely on their ability to self-diagnose liver damage or stomach bleeding. The comment also refuted the agency's evaluation of data relating to consumers' perception of label warnings, cited in the proposed rule (62 FR 61041 at 61051), suggesting that a general alcohol warning is less likely to prompt consumers into appropriate action than an explicit warning. The comment said the study was not designed to determine consumer understanding of the warnings tested and that flaws in that study prevent meaningful conclusions. The comment submitted no data to support its contention.

The agency considers organ specific warnings to be more effective than general warnings. Consumers are better equipped to make a decision on whether to take a medicine or contact their doctor when they know the specific risk involved. The agency believes that consumers with a history of heavy alcohol use need to know the potential risk of OTC analgesic/antipyretic use. If consumers are not advised of what may happen (liver damage or stomach bleeding) or what to do (ask their doctor), the agency believes they would be less likely to take the warning seriously or to consult their doctor.

13. Two comments recommended that the proposed warning be formatted in a style that more closely follows the February 27, 1997 (62 FR 9024), proposed rule on OTC label format. One comment contended that the use of specific headers for specific warnings are unnecessary and redundant. Also, specific warnings take up additional space, disrupt the logical flow of information, and distract from consumer

comprehension. No data were submitted by the comments.

The issue of labeling format for specific warnings is broader than this rulemaking which concerns a single alcohol warning. This issue will be addressed in a future issue of the **Federal Register** when the agency issues a final rule regarding labeling requirements for OTC drug products.

14. Several comments recommended reducing the maximum daily dose of acetaminophen to 2 grams (g) for heavy alcohol users but submitted no new data. Another comment supported the currently recommended maximum daily dose of 4 g acetaminophen.

The agency addressed this issue in the proposed rule (62 FR 61041 at 61044 to 61049) and evaluated a placebo-controlled, double-blind, randomized study of various dosages of acetaminophen in alcoholics (Ref. 71). The agency concludes that there is not sufficient evidence to recommend a specific dosage of acetaminophen which is safe and effective in subjects who use alcohol heavily.

15. One comment suggested that the acetaminophen labeling should warn against the use of more than one acetaminophen-containing product at a time. The comment also recommended that, because of overdose risk and risk of liver injury, acetaminophen preparations intended only for adults should contain warnings against use in children, and pediatric formulations should convey the need to follow instructions very carefully. The comment also noted that the warning does not address the effects of fasting on acetaminophen toxicity.

The issues raised by the comment are outside of this rulemaking which specifically addresses the need for an alcohol warning. However, the issues raised by the comment will be addressed in the final rule for OTC internal analgesic, antipyretic, and antirheumatic drug products in a future issue of the **Federal Register**.

16. One comment supported the agency's proposal and suggested that the warning should be put on the leaflet inside the package.

Information required to appear on the labeling by or under authority of section 502(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(c)) must be placed conspicuously so as to be read and understood by the consumer under customary conditions of purchase and use. Manufacturers may also include package inserts containing the required information, but such inserts are not required.

C. Comments on Product Exemptions

17. One comment maintained that enteric-coated products provide additional safety for aspirin users and urged FDA to recognize the documented health and safety benefits of enteric coatings on aspirin. The comment said that the enteric-coating minimizes gastric irritation because the enteric-coating delays dissolution of aspirin in the acidic environment of the gastric lumen. The comment further argued that this delayed absorption reduces the intracellular accumulation of aspirin in the gastric mucosa that can lead to cellular injury. In support of this position, the comment included data from published clinical research (Refs. 72, 73, and 74) and cited references (Refs. 75 and 76) to demonstrate the safety of enteric-coated aspirin. Based on these arguments, the comment suggested the agency take one of the following actions: (1) Exempt enteric-coated aspirin from the proposed warning, (2) defer action on a warning for this dosage form until the agency can gather data that would challenge the documented benefits of enteric-coated aspirin, or (3) require a separate warning for enteric-coated products.

The agency disagrees with the comment. The data provided by the comments do not demonstrate the safety of enteric-coated dosage forms of aspirin in consumers with a history of heavy alcohol use. Furthermore, as previously discussed, aspirin's adverse GI effects are due both to direct local irritation (the Davenport mechanism) and to systemic effects which result in prostaglandin inhibition and platelet dysfunction (Refs. 10 and 13).

As discussed in comment 1 of section II.A of this document, enteric-coated dosage forms may exert less direct local effect on the gastric mucosa, but they are associated with the same risks (and benefits) of other systemically absorbed aspirin products (Refs. 4 and 51). J. P. Kelly et al. (Ref. 77) examined 550 cases of UGI bleeding confirmed by endoscopy and 1,202 controls in a multicenter case-control study. Multiple logistic regression analysis demonstrated a similar relative risk for plain, enteric-coated, and buffered aspirin at high (RR: 5.8–7.0) and low (RR: 2.6–3.1) doses. C. A. Silagy et al. (Ref. 78) examined the adverse effects of low-dose enteric-coated aspirin (100 mg/d) in 400 subjects 70 years or older for 12 months in a double-blind, randomized, placebo-controlled trial. Clinically evident GI bleeding occurred in the enteric-coated aspirin treated group but not in the controls. Clinically evident bleeding from any site and decreased hemoglobin levels were significantly greater ($p<0.05$) in the aspirin-treated group than in the control group. In summary, clinical trials demonstrate UGI bleeding in patients who also take enteric-coated aspirin products. Therefore, the agency will require an alcohol warning for these products.

18. One comment requested that antacid and aspirin combination products (highly buffered aspirin in solution) that produce sodium acetylsalicylate, sodium citrate, and carbon dioxide when added to water prior to ingestion, not bear an alcohol warning. In support of this request, the comment submitted data documenting the chemical characteristics and safety profile distinguishing these products from plain aspirin. These data were previously reviewed by the Panel (42 FR 35346 at 35417) and are not resummerized in this document.

The agency disagrees with the comment. The Panel believed there is no valid clinical evidence to support the claim that highly buffered aspirin for solution has significantly less potential to induce major GI hemorrhage than other dosage forms of aspirin (42 FR 35346 at 35471). The agency concurred in comment 31 of the proposed rule for OTC internal analgesics drug products that the direct toxic effects from the Davenport mechanism may be reduced, but not eliminated, in highly buffered aspirin-for-solution products (53 FR 46204 at 46220). In addition, the indirect effects on systemic prostaglandin inhibition still play an important role in the toxicity of such products. Therefore, the agency will require an alcohol warning for these products.

19. One comment contended that OTC analgesic/antipyretic drug products differ in their benefits and potential for injury, and that any proposal to change the current labeling on such products should be on a product-by-product basis. The comment argued that alcohol warnings are not appropriate for products intended for relief of mild to moderate symptoms associated with menstrual periods in teenagers, or for OTC highly buffered aspirin solution products indicated for overindulgence of food and drink.

The agency disagrees that these products should be exempt from the alcohol warnings. In comment 18 in section II.C of this document, the agency discusses the need for an alcohol warning for OTC highly buffered aspirin solution products. Concerning the need for warnings on products intended for relief of mild to moderate symptoms associated with menstrual periods in

teenagers, this population is not immune to heavy alcohol use as up to 32 percent of high school students have reported heavy drinking (Ref. 79).

D. Comments on Implementation

20. A number of comments objected to the agency's proposed 6-month implementation date for the final rule because of the potential economic impact of the rule based on that timeframe. One comment requested flexibility in considering the appropriate implementation period for all OTC analgesic/antipyretic drug products or, at minimum, for cough-cold products containing these ingredients. The comment contended that the seasonal nature of cough-cold products requires large inventory stockpiles and shipments prior to the cough-cold season. Therefore, depending on the time of year that the rule becomes final, significant inventory may need to be destroyed if products are not shipped with required labeling by the effective date. The comment stated that industry estimates indicate that the average time to redesign and produce new labeling is 9.25 months. Therefore, it would be impossible to comply with the proposed 6-month implementation period. Trying to force these changes more quickly could lead to labeling errors, resulting in consumer confusion, potential recalls, and unavailability of some products in the marketplace.

Although the agency has suggested stick-on labeling as a means to comply with the 6-month implementation date, one comment believed that this would not be practical or cost-effective for most combination cough-cold products. This comment further argued that current warnings dictated by monographs expend most of the available space on containers and cartons, leaving insufficient room for placement of a sticker containing the additional warnings.

Several comments urged the agency to coordinate the implementation of the alcohol warning with other labeling proposals impacting these products. One comment requested that the agency make the rule effective no sooner than the effective date of the final rule for a standardized OTC labeling format (62 FR 9024). The comment noted that the agency expects that the standardized labeling final rule will result in major format and content changes to current OTC product labeling. If the final rule for the alcohol warning is effective prior to the standardized format final rule, manufacturers will incur significant labeling costs for each of these rules separately. Another comment requested that FDA extend the implementation date to 12 months.

One comment stated that 8 months had already been expended to complete the addition of the voluntary warning on its acetaminophen products. The comment contended that 14 additional months would be required to implement the alcohol warning for all products covered by the final rule. The comment recommended that an effective date of 24 months be established for implementation of the final rule for affected products that have not been updated to include the voluntary warning suggested in the proposed rule, and 36 months for products that already comply with the voluntary warning.

Although the final rule will have an economic impact on some manufacturers, the agency believes that the potential benefits of the rule, including reduced risk of adverse effects, override any economic concerns (see section III.C of this document). In an attempt to minimize the economic impact, the agency has allowed for a 6-month implementation period and the use of supplementary labeling (e.g., stick-on labels) to comply with the final rule. Further, manufacturers that voluntarily included in their labeling the exact warning in the agency's proposed rule will be permitted to exhaust their inventory of labels. The agency believes that these measures will help reduce labeling costs that manufacturers will incur to make the required labeling changes. The agency concludes that a 6-month implementation period for the required warning will ensure that consumers have the most recent information for the safe and effective use of OTC analgesic/antipyretic drug products.

III. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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 has 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.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of $100 million (adjusted annually for inflation) in any 1 year.

The agency believes that this rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this rule is to add warning statements to the labeling of OTC drug products labeled for adult use that contain internal analgesic/antipyretic active ingredients. The added statements warn of the increased risk of adverse effects from the use of OTC analgesic/antipyretic drug products by individuals who consume three or more alcoholic drinks every day. This rule is intended to reduce the number of specific adverse events associated with the use of these products by such individuals.

A. Benefits

As described earlier in this document, FDA finds that individuals who routinely drink alcohol heavily (three or more drinks every day) should be specifically warned of risk associated with their use of OTC analgesic/antipyretic drug products. For example, both aspirin and other NSAID's carry a dose-related risk of GI bleeding. Alcoholics are also known to be at increased risk of liver damage and UGI bleeding. However, because UGI bleeding and liver damage are not unexpected in alcohol users, medical personnel may not routinely investigate the use of OTC drug products by patients presenting with these problems. Recently, in a number of cases, use of acetaminophen was found to be associated with pathognomonic hepatotoxic changes among heavy alcohol users and to be a contributing factor in their hospitalization. Many of these patients required an extended hospital stay.

FDA cannot quantify the expected benefits of this rule, because it lacks the data to conduct a quantitative risk assessment. The agency notes, however, that an estimated 11 million Americans, or about 5.5 percent of the U.S. population age 12 and older, are heavy drinkers and, therefore, at risk (Ref. 80). Because alcohol warnings on OTC analgesic/antipyretic drug products could reduce the number of hospitalizations of heavy alcohol users for hepatic damage and UGI bleeding, the potential benefits of the rule are substantial. For example, the cost of a 7-day hospital stay (the average length of stay in 1994 for an alcohol related discharge) is about $10,000 (Ref. 81). (Length of stay was calculated as

weighted average of alcohol first-listed hospital discharges. Cost of stay was estimated from the 1987 National Medical Expenditure Survey; cost was converted to 1995 dollars using the CPI–U (consumer price index--urban areas) for medical services.) If, among the 11 million consumers potentially at risk, this rule prevented even 500 hospital visits annually, the present value of the avoided costs would be about $75 million. (This assumes a 7 percent discount rate and an infinite time horizon.)

B. Costs

OTC drug products containing internal analgesic/antipyretic active ingredients, labeled for adult use, will require new labeling to incorporate the warning statements. The agency's Drug Listing System identifies 5,000 to 6,000 OTC analgesic/antipyretic drug products. Assuming an average of 3 stock keeping units (SKU's)/product, up to 18,000 SKU's will require the alcohol warnings. In its analysis of the proposed rule, FDA estimated the cost of redesigning a label at from $2,000 to $3,000/SKU. No industry comment questioned this estimate. Nevertheless, FDA now believes that the lower end of that range is more likely, because the added warning requires only a straight-forward text change without significant graphics redesign. Alternatively, a private-label manufacturer estimated that the shorter implementation period would add about $700/SKU. On the assumption that lost inventory cost for branded SKU's will be twice as high, or $1,400, and that the market share of branded and private label SKU's is 70 and 30 percent, respectively, the added cost will amount to about $900. Thus, FDA projects the total cost of the new warnings at about $3,000/SKU. Consequently, the estimated one-time cost of this rule is about $54 million. The actual cost may be lower, because the agency is allowing supplementary labeling (e.g., stick-on labeling), which could reduce inventory losses.

C. Small Business Impacts

The agency estimates that fewer than 75 OTC drug manufacturers will incur costs. FDA does not have data on the size distribution of these affected firms, but an analysis of an IMS America, Ltd. listing of OTC drug manufacturers indicates that approximately 70 percent of all identified OTC drug manufacturers employ fewer than 750 employees, which is the Small Business Administration's definition of a small pharmaceutical firm. Consequently, the agency finds that this rule may have a significant impact on some OTC drug manufacturers, including smaller firms and manufacturers of private label products. The effect on individual firms will vary with the number of the firm's SKU's that require relabeling and the size and cost of the firm's labeling inventory. Most small firms will not incur significant regulatory costs because they manufacture few affected SKU's and use less expensive labeling stock. On the other hand, smaller firms tend to keep relatively larger labeling inventories because of the volume price discounts offered by printers. These firms could experience relatively higher costs for lost inventories.

This rule will not require any new reporting or recordkeeping activities. Therefore, no additional professional skills are needed. No small entities commented on the impact of the proposed rule or suggested alternatives that would reduce the economic impact on their establishments.

D. Alternatives

The agency considered but rejected several less costly regulatory alternatives, because they would not provide adequate health and safety benefits. First, the agency considered extending the implementation period from 6 months to 1 year. This alternative would have saved an estimated $18 million due to smaller labeling inventory losses. Nevertheless, as stated in section II.D of this document, in comment 20, the required warnings are necessary to alert consumers to the potential for serious health outcomes. As the warnings provide consumers with the critical information needed for making informed decisions, the longer implementation phase-in would increase the period over which consumers may make inappropriate choices. The agency concluded that the reduced labeling cost associated with the longer phase-in would not justify the increased risk to the public health that would occur over the additional 6-month period.

The agency then considered permitting a 1-year implementation period for those products already labeled with less specific alcohol warnings. This alternative also was rejected, based on the agency's determination that most current warnings are inadequate, because they fail to address the specific nature of the adverse consequence.

E. Conclusion

The above cost estimates demonstrate that this rule is not economically significant under Executive Order 12866. As discussed previously, the agency concludes that this rule is the least burdensome alternative that meets the agency objective of providing the public with important health and safety information in a timely manner. As this rule may have a significant impact on a substantial number of small entities, this analysis, together with other relevant sections of this document, serve as the agency's regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, the Unfunded Mandates Reform Act does not require a cost-benefit analysis of this rule, because the rule will not result in an expenditure by State, local, or tribal governments, in the aggregate, or by the private sector of $100 million in any 1 year.

IV. Paperwork Reduction Act of 1995

FDA concludes that the warning statement set forth in this document is not subject to review by the Office of Management and Budget because it does not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*) Rather, the required warning statement is 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)).

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

VI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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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 201.322 is added to subpart G to read as follows:

§ 201.322 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required alcohol warning.

(a) People who regularly consume large quantities of alcohol (three or more drinks every day) have an increased risk of adverse effects (possible liver damage or gastrointestinal bleeding). OTC drug products containing internal analgesic/antipyretic active ingredients may cause similar adverse effects. FDA concludes that the labeling of OTC drug products containing internal analgesic/antipyretic active ingredients should advise consumers with a history of heavy alcohol use to consult a physician. Accordingly, any OTC drug product, labeled for adult use, 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 shall bear an alcohol warning statement in its labeling as follows:

(1) *Acetaminophen*. ''Alcohol Warning'' [heading in boldface type]: ''If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.''

(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.* ''Alcohol Warning'' [heading in boldface type]: ''If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [insert one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient] or other pain relievers/fever reducers. [Insert one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient] may cause stomach bleeding.''

(3) *Combinations of acetaminophen with 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. ''Alcohol Warning'' [heading in boldface type]: ''If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [insert acetaminophen and one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate] or other pain relievers/fever reducers. [Acetaminophen and (insert one nonsteroidal anti-inflammatory analgesic/antipyretic ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate] may cause liver damage and stomach bleeding.''

(b) *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 warning in the product's labeling. Such labeling may be put into use without advance approval of FDA provided it includes the exact information included in paragraph (a) of this section.

(c) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after April 23, 1999, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and is subject to regulatory action.

Dated: July 22, 1998.

Michael A. Friedman,

Acting Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 98–28520 Filed 10–21–98; 10:58 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 343

[Docket No. 77N–094A]

RIN 0910–AA01

Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-The-Counter Human Use; Final Rule for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination With Antacid Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing as a final rule professional labeling for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic drug products containing aspirin, buffered aspirin, and aspirin in combination with an antacid. This portion of the final monograph is being issued prior to the entire monograph so that the professional labeling of these products will reflect the latest information on cardiovascular, cerebrovascular, and rheumatologic uses. FDA is issuing this final rule after considering comments on the agency's proposed regulation for OTC internal analgesic, antipyretic, and antirheumatic drug products, a proposed amendment to the regulation, and data and information that have come to the agency's attention.

EFFECTIVE DATE: October 25, 1999.

FOR FURTHER INFORMATION CONTACT: Ida I. Yoder, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 16, 1988 (53 FR 46204), FDA published, under 21 CFR 330.10(a)(7), a notice of proposed rulemaking, in the form of a tentative final monograph (TFM), that would establish conditions in part 343 (21 CFR part 343) under which OTC internal analgesic, antipyretic, and antirheumatic drug products are generally recognized as safe and effective and not misbranded. In the TFM (53 FR 46204 at 46258 and 46259), the agency proposed professional labeling in § 343.80 for the use of aspirin for rheumatologic diseases, for reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli, and for reducing the risk of death and/or nonfatal myocardial infarction (MI) in patients with a previous infarction or unstable angina pectoris. The agency also proposed professional labeling for the use of carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate for rheumatologic diseases. Interested persons were invited to submit new data or file written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal.

In response to the TFM, the agency received four comments and three citizen petitions related to the professional labeling of aspirin for cardiovascular and cerebrovascular uses (Ref. 1). No comments were received on the professional use of aspirin drug products for rheumatologic diseases. In response to two of the petitions, the agency proposed to amend the professional labeling section of the TFM for OTC internal analgesic, antipyretic, and antirheumatic drug products to include an indication for aspirin for suspected acute MI (61 FR 30002, June 13, 1996). In response to the proposed amendment, the agency received 10 comments (Ref. 2).

In the TFM for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204 at 46205), and in the proposed amendment to the TFM (61 FR 30002), the agency proposed that any final rule that may issue based on the proposal will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after October 25, 1998, the dissemination of professional labeling that does not comply with this final rule may result in regulatory action against the product, the marketer, or both. Manufacturers are encouraged to comply voluntarily with this final rule at the earliest possible date.

The labeling in this final rule for professional use of aspirin drug products contains complete information on certain professional uses of aspirin, including information for professionals on the treatment of the signs and symptoms of rheumatologic disease. The labeling is organized and presented in a manner similar to that required of prescription drug products under §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57). The labeling in this final rule also includes an optional highlights section that summarizes the professional indications and the recommended dosage and