described previously in this document. For example, the new law gives FDA express authority to require marking on any food product that had been refused admission into the United States whereas the proposed rule would have required marking on food refused admission for safety reasons only.

The new law also significantly revises section 801(d)(3) of the act; it prescribes new reporting requirements that differ from those in the FDA proposed rule.

Because of the changes brought about by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, FDA is withdrawing both proposed rules. FDA will consider whether new rulemakings or other actions are necessary to implement the new statutory requirements.

Dated: August 13, 2002.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 02–21264 Filed 8–20–02; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 02N–0241]

Amendment of Regulations on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a proposed rule that appeared in the **Federal Register** of August 12, 2002 (67 FR 52429). The document proposed to amend FDA's regulations to change the labeling requirements concerning aluminum in small volume parenterals and pharmacy bulk packages used in total parenteral nutrition. The document was published with an inadvertent error. This document corrects that error.

DATES: Submit written or electronic comments by October 28, 2002.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments at http://www.fda.gov/dockets/ecomments. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Doris B. Tucker, Office of Policy, Planning, and Legislation (HF–27), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7010.

SUPPLEMENTARY INFORMATION: In FR Doc. 02–20300, appearing on page 52429 in the **Federal Register** of Monday, August 12, 2002, the following correction is made:

1. On page 52429, in the third column, in the seventh line ''§ 201.323©'' is corrected to read ''§ 201.3239(c)''.

Dated: August 15, 2002.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 02–21265 Filed 8–20–02; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 343

[Docket No. 77N–094I]

RIN 0910–AA01

Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph, and Related Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the tentative final monograph (TFM) for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic (IAAA) drug products to include ibuprofen as a generally recognized safe and effective analgesic/antipyretic active ingredient for OTC use. FDA is also proposing to amend its regulations to include consistent allergy warnings for OTC IAAA drug products containing nonsteroidal anti-inflammatory active ingredients. These proposals are in response to a citizen petition (Ref. 1) and to a comment submitted in response to that petition (Ref. 2) and are part of the ongoing review of OTC drug products conducted by FDA.

DATES: Submit written or electronic comments by November 19, 2002. Submit written or electronic comments on the agency's economic impact determination by November 19, 2002. Please see section XII of this document for the effective date of any final rule that may publish based on this proposal.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

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:

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I. Background

Ibuprofen is benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-, a member of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAIDs). The commercially available drug is a racemic mixture of two optical isomers (S-[+] and R-[-] ibuprofen). The racemic mixture is recognized in the U.S. Pharmacopeia (U.S.P.) (Ref. 3). Ibuprofen has been available as a prescription drug for the treatment of osteoarthritis and rheumatoid arthritis at a dose of 1,200 to 3,200 milligrams (mg) per (/) day since 1974 in the United States and since 1969 in the United Kingdom. Ibuprofen has also been marketed by prescription and OTC in numerous countries throughout the world (Ref. 4).

Safety and effectiveness data submitted to the agency to support the approval of the OTC marketing of a 200-mg ibuprofen tablet were considered by the Arthritis Advisory Committee (AAC)

at its August 18, 1983, meeting. Based on the available data, the AAC concluded that a 200-mg ibuprofen product could be used safely and effectively OTC, without the supervision of a physician (Ref. 5). It has been available on the OTC market for use in adults and children 12 years and older since 1984 through the new drug application (NDA) process. It is marketed at a 200-mg dosage strength, for the relief of minor aches and pains and for fever reduction. A single OTC dose is 200 to 400 mg with a maximum daily dose of 1,200 mg.

The AAC suggested warnings and precautions that it believed should appear in labeling to alert individuals to certain risks, especially those individuals who should not use ibuprofen without the supervision of a physician. The AAC was concerned that the promotion of OTC ibuprofen not counteract a warning regarding ibuprofen's cross-reactivity with aspirin (Ref. 5). The agency's approved labeling for ibuprofen includes warnings for aspirin sensitive individuals and people taking other OTC pain reliever/fever reducer products (Ref. 6).

On October 17, 1983, a citizen petition (Ref. 7) was submitted that requested the agency to reopen the administrative record for OTC IAAA drug products to amend the proposed monograph to include ibuprofen as an internal analgesic ingredient in a 200-mg tablet with a maximum 1,200-mg total daily dose. The agency denied the petition on May 18, 1984 (Ref. 8) for several reasons, one of which (use for a material time and to a material extent) is discussed in section III.A of this document.

In the **Federal Register** of November 16, 1988 (53 FR 46204), the agency published a TFM to establish conditions under which OTC IAAA drug products are generally recognized as safe and effective, and not misbranded. The TFM proposed acetaminophen, aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, and sodium salicylate as generally recognized as safe and effective IAAA active ingredients for OTC use and appropriate labeling for OTC drug products containing these ingredients. Ibuprofen was not discussed in the TFM.

Subsequent to the TFM, the agency received a citizen petition (Ref. 1) requesting that the TFM be amended to include racemic ibuprofen in an oral dosage form, as a single active ingredient. The petition recommended a minimum effective dose of 200 mg ibuprofen for use by adults and children 12 years and older. The petition requested the same indications as proposed for other monograph IAAA active ingredients in § 343.50(b)(1) (21 CFR 343.50(b)(1)): ''For the temporary relief of minor aches and pains associated with a cold, sore throat, headache, toothache, muscular aches, backache, premenstrual and menstrual cramps (dysmenorrhea), and for the minor pain from arthritis, and to reduce fever.''

The petition requested warnings specific for the OTC use of ibuprofen, including the following warning, in this form, or in a different format conveying the same information:

ASPIRIN SENSITIVE PATIENTS: Although this product does not contain aspirin, it may cause a severe reaction in people allergic to aspirin. Do not take ibuprofen if you have had any of the following reactions to any pain reliever/fever reducer:

- allergic reaction
- shock
- hives
- difficulty breathing
- asthma
- swelling

If you are under a doctor's care for any serious condition, consult a doctor before taking this product. As with aspirin and acetaminophen, if you have any condition which requires you to take prescription drugs or if you have had any problems or serious side effects from taking any nonprescription pain reliever, do not take this product without first discussing it with your doctor. IF YOU EXPERIENCE ANY SYMPTOMS WHICH ARE UNUSUAL OR SEEM UNRELATED TO THE CONDITION FOR WHICH YOU TOOK IBUPROFEN, CONSULT A DOCTOR BEFORE TAKING ANY MORE OF IT. Although ibuprofen is indicated for the same conditions as aspirin and acetaminophen, it should not be taken with them except under a doctor's direction. Do not combine this product with any other ibuprofen-containing product.

The petition also suggested the following directions for use:

Adults: Take 200 mg every 4 to 6 hours while symptoms persist. If pain or fever does not respond to 200 mg, 400 mg may be used but do not exceed 1,200 mg in 24 hours, unless directed by a doctor. The smallest effective dose should be used. Take with food or milk if occasional and mild heartburn, upset stomach, or stomach pain occurs with use. Consult a doctor if these symptoms are more than mild or if they persist. Children: Do not give this product to children under 12 years of age except under the advice and supervision of a doctor.

The petition asserted that ibuprofen has been marketed for a material time and to a material extent. To support this statement, the petition presented information indicating that from May 1984 (when ibuprofen first became available OTC in the United States) through 1996 over 90 billion 200-mg tablet doses were sold (Ref. 1). The petition noted that more than 20 companies now market OTC ibuprofen drug products and provided information to show that the sale of OTC ibuprofen in the United States is comparable to that of aspirin and acetaminophen. Thus, the petitioner said, given the enormous volume of sales and more than 13 years of marketing, ibuprofen has been available as an OTC drug product for a material time and to a material extent, is now generally recognized as safe and effective, and is no longer a new drug. The petition did not request monograph status for ibuprofen for children under 12 years of age.

The petition (Ref. 1) included a summary of safety and effectiveness data (through 1982) previously submitted to FDA to support the prescription-to-OTC switch of ibuprofen. That summary included effectiveness data for ibuprofen for analgesic (dysmenorrhea, dental, musculoskeletal, postpartum and postsurgical pain, and headache), antipyretic, and anti-inflammatory use and a safety overview of specific organ systems, special populations, and postmarketing data. The petition (Ref. 1) also included the results from a search of the worldwide medical literature from 1983 through August 1996 of adverse events associated with ibuprofen, mostly in the OTC dosage range.

The published studies and case reports included in the petition involved mainly OTC doses of ibuprofen (less than or equal to 1,200 mg/day) for an OTC-indicated duration (less than 10 days use for pain, or 3 days for fever) that occurred in generally healthy individuals, 12 years of age or older. The agency's comments on the citizen petition are on file in the Dockets Management Branch (Ref. 9). The petitioner subsequently submitted additional information in support of ibuprofen's safety profile (Ref. 10), which included publications from 1990 through 1998, generated from a number of databases.

The agency also received a comment opposing the petition's request to include ibuprofen in the TFM (Ref. 2). The petition, related correspondence, additional information, and the opposing comment are on public

display in the Dockets Management Branch (see **ADDRESSES**).

II. Comment in Opposition to the Citizen Petition

One comment (Ref. 2), opposing the petition's request, stated there is: (1) A lack of a general recognition of safety and effectiveness of all oral ibuprofen dosage forms, (2) a significant potential for use of OTC ibuprofen products at prescription dosage levels, and (3) a continued need for adverse event reporting and other marketing controls. Therefore, the comment contended, ibuprofen (200 mg) should remain subject to the NDA process.

The comment suggested that allowing marketing of ibuprofen (200 mg) in any ''suitable'' oral dosage form (as provided for in the TFM) creates a potential for consumer harm. As examples, the comment mentioned several risks if ibuprofen would be included in the monograph: (1) Changes in product composition and manufacturing methods that would not be subject to prior FDA review, and (2) possible misuse of ibuprofen products due to the concurrent marketing of ibuprofen suspensions (one marketed under a monograph for adults and the other marketed under the new drug approval process and labeled for children).

The comment also criticized the data included in the petition. The comment observed that although data on adverse events in prescription dosages is relevant to the consideration of whether an ingredient is appropriate for inclusion in the monograph, the petition submitted only information on adverse effects at OTC doses. The comment asserted that ingestion of larger doses (2,400 to 3,600 mg) has not been seen due to the relative expense of the OTC tablets. The comment contended that the lowered prices that would result from monograph status of ibuprofen (200 mg) could increase the potential for harm because prescription ibuprofen users may be enticed to switch to OTC drug products and self-medicate at prescription dose levels without a doctor's supervision. The comment did not provide any data to support its assertions.

The agency agrees with the opposing comment (Ref. 2) that ibuprofen is not generally recognized as safe and effective in all dosage forms. For instance, ibuprofen in suspension formulation for adult use has not been marketed OTC, and children's formulations have been marketed OTC less than 5 years. Thus, these formulations are not generally recognized as safe and effective for OTC use. In some studies evaluating the effectiveness of ibuprofen, capsule formulations were used as a means of blinding the studies. However, ibuprofen has been marketed OTC for adult use almost entirely in tablet formulations (i.e., tablets, caplets, and gelcaps (a tablet dosage form)) throughout its marketing history. Thus, current evidence for ibuprofen to be generally recognized as safe and effective for OTC use is only sufficient for tablet formulations. This proposal does not include liqui-gel formulations (ibuprofen solubilized in a gel matrix).

The comment raised a concern about the potential for OTC ibuprofen to be used at prescription-dose levels. Currently approved NDA and abbreviated new drug application (ANDA) labeling for OTC ibuprofen drug products contains directions for appropriate OTC dosing. Products marketed under an OTC drug monograph will contain the same directions. Further, both the NDA/ANDA and the proposed monograph labeling alert consumers of the hazards associated with improper use and when to seek the advice of a physician. Given that the comment did not include any data to support its concern, the agency finds no basis to believe that the potential for misuse of these OTC ibuprofen drug products will be greater if their marketing status is changed from an NDA/ANDA to OTC drug monograph.

The agency appreciates the comment's concern for the need for continued adverse event reporting and other marketing controls. The safety of ibuprofen has been monitored since it was first marketed in the United States under the new drug approval process (as a prescription drug in 1974 and as an OTC drug in 1984) and as a generic drug (for prescription use in 1985 and for OTC use in 1986). The agency monitors the quality of products marketed under OTC drug monographs through its current good manufacturing practice regulations in part 211 (21 CFR part 211) and its inspection authority. Based on the available data, the agency finds the safety profile of ibuprofen to be comparable to that of other OTC internal analgesics (e.g., aspirin and acetaminophen) that have been proposed as generally recognized to be safe for OTC use.

During ibuprofen's extensive OTC marketing history significant formulation and manufacturing issues have not arisen. The agency does not anticipate any potential problems if ibuprofen, in specific tablet formulations, is included in the monograph for adult use. Specifications for ibuprofen tablets are recognized in the U.S.P. (Ref. 3). Although there is some degree of risk associated with the use of any OTC drug, whether marketed through the NDA/ANDA process, as a generic drug, or under an OTC drug monograph, the agency believes ibuprofen 200 mg in a tablet dosage form for adult use has been marketed safely OTC for a sufficient time and extent that it can be generally recognized as safe and effective for OTC use.

III. The Agency's Evaluation of the Citizen Petition

A. Use for a Material Time and to a Material Extent

In 1984, the agency denied a petition (Ref. 7) to include ibuprofen in the OTC IAAA monograph because the request was for a new dosage strength (200 mg) which the agency determined had not been used to a material extent and for a material time in the United States and, thus, was considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The petitioner had contended that ibuprofen had been available in the United States since 1974 as a prescription drug with more than 18.8 billion cumulative 400-mg doses of the drug distributed worldwide through August 1982, and that the drug is currently the fourth largest prescription drug by volume in the United States. In its denial letter (Ref. 8), the agency pointed out that experience with ibuprofen at prescription strength is pertinent to the drug's safety, but such experience cannot support general recognition that the product, at a different strength and daily dose, can be used safely and effectively by the patient alone. The agency concluded that the petition ignored the lack of experience with the proposed single 200-mg tablet dose as an OTC drug product.

Since that time, the current petition (Ref. 1) points out that from May 1984 (when ibuprofen 200-mg first became available OTC in the United States) through 1996 over 90 billion 200-mg tablet doses were sold. That number has substantially increased since 1996. The agency has determined that ibuprofen's 17 years of OTC marketing with over 100 billion doses of 200-mg tablets sold shows that the drug at this dosage and in this dosage form as an internal analgesic and antipyretic has been used for a material time and to a material extent to qualify it for inclusion in an OTC drug monograph.

B. Safety

1. Preclinical

a. *Toxicity*. The toxicity of ibuprofen has been extensively studied in a number of animal species (Refs. 11 and 12) and well characterized. The LD_{50} in the mouse was 800 mg/kilogram (kg) orally and 320 mg/kg intraperitoneally. In rats, the LD_{50} was 1,600 mg/kg orally and 1,300 mg/kg subcutaneously. In dogs, adverse effects were observed after a single oral dose of 125 mg/kg. There were no apparent ill effects after a single 20 or 50 mg/kg dose. Ibuprofen in lethal doses depressed the central nervous system of rodents, and was ulcerogenic in rodents and nonrodents.

Newly weaned male and female rats were given 180, 60, 20, and 7.5 mg/kg/day ibuprofen by oral gavage for 26 weeks (Ref. 12) . Rats receiving ibuprofen grew normally except for male rats receiving the 180-mg/kg/day dose which gained significantly less weight than controls. When examined hematologically in the final week of dosing, both males and females on the 180 mg/kg/day dose were anemic as evidenced by low erythrocyte counts, hemoglobin concentrations, and hematocrits. Significant increases in the weights of the kidney, liver, and spleen occurred in both sexes. Histologic examination of the tissues revealed no significant changes except for one male and three female rats in the 180-mg dose group (10 animals/sex/group) that had intestinal ulcers.

In a followup experiment (Ref. 12) to determine if the changes observed in the 26-week study were reversible, male and female rats were given 180, 60, and 20 mg/kg/day for 13 weeks. The day after dosing ended, half the animals in each group were sacrificed and the rest were kept undosed for 3 weeks. Generally, the results from this experiment were supportive of the 26-week study. Males given 180 mg/kg/day had enlarged kidneys, spleen, and testes. A dose-dependant enlargement of the kidney occurred in females. An enlargement of the liver and ovaries occurred in females on 180 mg/kg/day, and of the spleen and ovaries in females on 60 mg/kg/day. None of the enlarged organs were histologically abnormal. These changes were found to be reversible 3 weeks after the end of dosing.

No significant hematological or biochemical alterations were observed in dogs (two dogs/sex/group) given 16, 4, or 2 mg/kg/day ibuprofen (administered as two doses 6 hours apart) for 26 weeks (Ref. 12). In the eighth week of dosing, female dogs in the high-dose group showed gross signs of gastrointestinal (GI) disturbance characterized by frequent vomiting, diarrhea (with occasional passage of fresh blood), and loss of blood. Occult blood was irregularly detected in fecal samples obtained from all dogs in the high-dose group from day 8 on. At autopsy, organ weights were normal and pathologic changes were limited to ulcerative lesions of the GI tract.

The effects of ibuprofen on reproduction have been studied in rats and rabbits (Ref. 12). Rats were administered 180, 60, 20, or 7.5 mg/kg/day ibuprofen on days 1 through 20 of pregnancy. All litters were of normal size and weight. No difference in the incidence of fetal malformations was found between the treated and control groups.

A reproduction study in rabbits (Ref. 12) at doses of 60, 20, or 7.5 mg/kg/day was conducted on days 1 through 29 of pregnancy. Female rabbits given 60 mg/kg/day had fewer live fetuses per litter than did controls, but there was no significant difference in the number of dead and resorbed rabbits per litter. However, there was a reduction in the ratio of implants to corpora lutea, which suggested that the decrease in live litter size was due to interruption of early pregnancy. The average fetal weight was normal. At the lower doses, the litter size was unaffected. Apart from four young in one litter (60 mg/kg/day) with multiple malformations characteristic of cyclopia, there was no consistent pattern of dose-related malformations. The authors concluded that ibuprofen is not teratogenic but may reduce fertility by affecting early pregnancy at the high dose.

The labeling of ibuprofen drug products currently marketed under an NDA/ANDA includes the general pregnancy/breast-feeding warning in § 201.63(a) (21 CFR 201.63(a)) advising that a health professional should be consulted before use. It also includes a statement like that required for aspirin drug products in § 201.63(e), which warns that it is especially important not to use the product during the third trimester of pregnancy because it could cause problems in the unborn child and complications during delivery. The agency is proposing to expand the warning in § 201.63(e) to include ibuprofen. (See section V, number 1 of this document.)

b. *Pharmacokinetics*. Ibuprofen's mode of action is not completely understood, but it may be related to its ability to inhibit prostaglandin synthetase (Ref. 13). Following oral dosing, ibuprofen has been found in synovial fluid, which is the proposed site of action for ibuprofen in patients with rheumatoid arthritis (Ref. 14). The pharmacologic activity of ibuprofen has been attributed mostly to the S-[+]-enantiomer (Refs. 15 and 16). After administration of racemic ibuprofen, the inactive R-[-]-enantiomer is slowly and incompletely (60 percent) converted to the biologically active S-[+]-enantiomer, primarily through both presystemic and systemic chiral inversion (Refs. 17, 18, and 19).

The pharmacokinetics of ibuprofen have been well documented (Ref. 20). The absorption of orally administered ibuprofen is rapid and approximately 80 percent of the dose is absorbed from the GI tract. Peak plasma levels in humans are reached between 45 and 90 minutes after administration of a single oral dose on an empty stomach, depending upon the formulation (Ref. 21). The extent of absorption is unchanged when ibuprofen is taken with meals (Ref. 22).

Following oral administration, the apparent plasma volume of distribution has been reported to be between 0.1 to 0.2 liter (L)/kg, which approximates plasma volume and suggests minimal tissue binding is present (Refs. 23 and 24). Ibuprofen is extensively bound (more than 98 percent) to whole human plasma and purified serum albumin at therapeutic concentrations, and may participate in plasma protein binding displacement reactions (Refs. 25 and 26). The apparent volume of distribution, based on total concentration, increases significantly with dose, but there is no attendant change in free drug volume of distribution (Ref. 27). The protein binding of ibuprofen is similar between normal individuals and people with osteoarthritis and rheumatoid arthritis and is not influenced by age or gender (Refs. 28 and 29).

Plasma concentrations of ibuprofen appear to decline in a biphasic manner with a plasma half-life of 2 to 4 hours for the racemate (Ref. 20). Ibuprofen is metabolized via oxidation by the cytochrome P–450 enzyme CYP 2C9 to form two inactive metabolites, hydroxy- and carboxypropyl-phenylpropionic acid (Refs. 30 and 31). These metabolites (or their glucuronide conjugates) are excreted in the urine and account for about 50 to 60 percent of the oral dose administered (Refs. 32 and 33). Less than 10 percent of the drug is excreted in urine unchanged (Ref. 32). The remainder is eliminated in the feces, as metabolites and unabsorbed drug. Excretion of ibuprofen is essentially complete within 24 hours following oral administration of a single dose (Ref. 33). While total clearance may be affected by age, no dosage adjustment is needed in the elderly (Ref.

34). Ibuprofen does not appear in the breast milk of mothers to any appreciable extent (i.e., < 0.0008 percent of the plasma level) (Ref. 35).

Ibuprofen is neither an inducer or an inhibitor of cytochrome P–450 mediated metabolism. At doses above those recommended for OTC use (1,200 mg daily, in divided doses), ibuprofen may decrease the renal excretion of some drugs due to ibuprofen's ability to interfere with renal prostaglandin synthesis necessary for normal renal function. This interference in the renal elimination of other drugs can be estimated by following the net reduction in creatinine clearance. Ibuprofen can cause an increase in blood pressure in hypertensive patients being treated with diuretics alone or diuretics combined with other agents (Ref. 36).

2. Clinical Data

The petition (Ref. 1) and a subsequent submission (Ref. 10) provided extensive published clinical data on the safety of OTC use of ibuprofen. The data provide a safety profile typical of other OTC drugs in the NSAID class.

a. *Gastrointestinal.* The GI tract is one of the major organ systems commonly affected by NSAID-induced drug toxicity. This resulted in a GI warning in the prescription labeling for these drugs (Refs. 37 and 38). At the August 18, 1983, AAC meeting, data submitted in support of the NDA for ibuprofen 200 mg to be marketed as an OTC drug product suggested that, of all NSAIDs available at that time, ibuprofen caused the least amount of GI irritation (Ref. 39).

Additional support in favor of ibuprofen's overall gastric tolerability was generated in a recent study by Moore et al. (Ref. 40), which evaluated the tolerability of ibuprofen (1,200 mg/day) and acetaminophen (up to 3 grams (g)/day) to that of aspirin (up to 3 g/day). This study was a large, blinded, randomized, multicenter, 7-day analgesic study conducted in France in 8,677 adults with mild to moderate pain due to a variety of conditions. Although the incidence for significant (serious, severe, or moderate) adverse events (including all body systems) for the ibuprofen treated group (13.7 percent) was comparable to that of the acetaminophen treated group (14.5 percent), both drugs were shown to be significantly better tolerated than aspirin (18.7 percent; $p < 0.001$ via a one-sided 96.5 percent confidence interval (CI)). A total of six subjects reported having GI bleeds during this study, four from the acetaminophen group and two from the aspirin group, one of whom developed peptic ulcer. Overall, treatment with ibuprofen was associated with fewer significant adverse GI events than aspirin ($p < 0.001$) or acetaminophen ($p < 0.02$). The incidences of abdominal pain and dyspepsia were both significantly lower in the ibuprofen group as compared with the aspirin ($p < 0.001$) or acetaminophen ($p < 0.02$) groups. Although this study was designed to approximate the general population who would use OTC doses and durations of these three analgesics, its selection criteria prohibited any individual with known risk factors for GI bleeding from participating. Thus, selection bias may have been introduced and resulted in a lower incidence of GI adverse events than what may be seen in the general population at risk.

In a retrospective, nested, case-controlled study of Medicaid enrollees, Griffin et al. (Ref. 41) compared the relative risk (RR) for the development of peptic ulcer disease (PUD) in 1,415 subjects 65 years and older who were current nonaspirin NSAID users to nonusers. Eighty-three of the 1,415 subjects who were hospitalized due to PUD during the period studied were identified as having been exposed to OTC doses (1,200 mg) of ibuprofen. The overall RR for the development of PUD in this group was found to be 2.3 (95 percent CI: 1.8 to 3.0). Further examination by dose revealed that in 70 subjects exposed to doses less than 2,400 mg ibuprofen the RR for the development of PUD was 2.2 (95 percent CI: 1.7 to 2.9), and in 13 subjects exposed to 2,400 mg or greater the RR increased to 3.3 (95 percent CI: 1.7 to 6.5).

Bradley et al. (Ref. 42) conducted a 4-week, double-blind, randomized trial in 184 subjects comparing the effectiveness and safety of the maximum approved OTC daily dose of 1,200 mg of ibuprofen (number of subjects (n) = 62) to that of a prescription dose of 2,400 mg/day (n = 61), and to 4,000 mg/day of acetaminophen (n = 59) for the treatment of osteoarthritis. While there were no significant differences in the number of side effects reported during this study, the study demonstrated a trend towards a dose-dependent increase in minor GI adverse events (nausea and dyspepsia) associated with higher doses of ibuprofen (1,200 mg/day: 7/62 or 11.3 percent; versus 2,400 mg/day: 14/61 or 23 percent). In addition, two subjects treated with 2,400 mg/day of ibuprofen became positive for occult blood while participating in the study.

Although these studies (Refs. 41 and 42) demonstrate that a dose-dependent relationship exists for ibuprofen-induced gastrotoxicity, the number of subjects exposed to OTC doses of ibuprofen (1,200 mg or less a day) is too small to draw valid conclusions. Further, the study results may also be confounded since the studies did not control for other risk factors (i.e., smoking, alcoholism, concomitant use of corticosteroids and anticoagulants, advanced age, prior history of PUD, or deteriorated general health status) which are known to increase the risk of developing GI bleeding while using NSAIDs. In addition, the results of the retrospective study (Ref. 41) may be biased because the exposure data from that study were generated from records of prescriptions written for both the study and control populations rather than what was actually used by the subjects.

In a matched, case-controlled, international study of upper gastrointestinal bleeding (UGIB), Kaufman et al. (Ref. 43) evaluated the association between regular and occasional NSAID use and the risk of major UGIB in subjects hospitalized with their first major UGIB. Subjects were asked about their history of NSAID use, and details of timing, duration, frequency, and the daily dose of each episode of use. The focus of the data analysis was on NSAID use in the week immediately before the day of onset of bleeding. Exposure was defined as any use in the week before the index day. No evidence of an association of gastric bleeding with either regular use (n = 9; RR: 1.0 [95 percent, 0.4 to 2.6]) or occasional use (n = 14; RR 1.1 [95 percent, 0.5 to 2.4]) of ibuprofen was identified in this study. Among the cases of gastric bleeding, the median ibuprofen dose was 2,332 mg. The RR for developing a duodenal bleed with regular use (n = 7) of ibuprofen was 2.4 (95 percent, 0.5 to 11), the median daily ibuprofen dose ingested was 1,074 mg.

Strom et al. (Ref. 44) did a retrospective, case-controlled study in a Medicaid population generated database and evaluated the risk of developing GI bleeding associated with the use of OTC-simulated doses of naproxen sodium (600 mg/day or less) versus ibuprofen (1,200 mg/day or less). (At the time of the study, naproxen sodium was not yet approved for OTC use.) Although this study demonstrated that the overall incidence of UGIB associated with either the use of naproxen sodium [0.026 percent (95 percent CI, 0.017 percent to 0.038 percent)] or ibuprofen [0.012 percent (95 percent CI, 0.008 percent to 0.017 percent)] at simulated OTC doses was relatively low, the RR for developing an UGIB was approximately twofold higher for the

naproxen sodium cohort [2.0 (95 percent CI, 1.1 to 3.8)] as compared to the ibuprofen cohort. The study also showed that the RR for developing UGIB is increased in subjects who ingest multiple NSAIDs at OTC doses [4.1 (95 percent CI, 1.2 to 13.8)].

Endoscopic data (Refs. 45 and 46) demonstrated that while ibuprofen produced less GI mucosal toxicity or gastric injury than other NSAIDs, low doses of ibuprofen produced lesions in some subjects. In a study by Bergmann et al. (Ref. 45), endoscopic lesions of 12 healthy volunteers were evaluated after the administration of single doses of ketoprofen (25 mg), ibuprofen (200 mg), and aspirin (500 mg), and rated on a scale of 0 to 4. Endoscopic scores for ketoprofen were comparable to those for ibuprofen. After a single dose of ibuprofen 200 mg, eight subjects had endoscopic scores of 0, one had a score of 1, and three had scores of 2. For ketoprofen, nine subjects had a score of 0, two had a score of 2, and one had a score of 3.

Lanza (Ref. 46) conducted an endoscopic study of normal volunteers without histories of PUD. Subjects were prohibited from using alcohol and other NSAIDs for the week before and during the study. Ingestion of 1,200 mg/day of ibuprofen for 7 days produced a gastric injury score of 0.46 (on a scale of 0 to 4) and a 0 ulcer incidence rate in the 13 subjects studied. However, an increase in the ibuprofen dose to 1,600 mg/day for 7 days under the same conditions produced ulcers in 5 out of the 55 (9.1 percent) subjects studied, and an injury score of 1.24.

A chromium 51-labeled fecal blood loss study (Ref. 47) indicated that after 5 days of treatment with either ibuprofen 1,500 mg/day, aspirin 1,500 mg/day, lysine clonixinate 375 mg/day, or placebo, the fecal blood loss in subjects treated with ibuprofen was significantly less than the aspirin treated group. Nevertheless, treatment with ibuprofen lead to a small increase in mean daily blood loss of +0.52 milliliter (mL)/day.

These studies indicate that ibuprofen, at OTC doses, has a low level of GI toxicity but is not entirely devoid of such toxicity. The agency believes that even this low level of toxicity could increase the risk of GI bleeding in people who have other risk factors for developing GI bleeding. Therefore, the agency is proposing including a warning in the labeling of OTC ibuprofen to alert individuals at risk for GI problems associated with the use of the product. The warning would include: ''Ask a doctor before use if you have: • stomach problems that last or come back, such as heartburn, upset stomach, or pain • ulcers • bleeding problems''.

b. *Renal*. NSAIDs affect renal physiology by inhibiting cyclo-oxygenase and the synthesis of vasodilatory prostaglandins resulting in acute intrarenal hemodynamic changes that can cause reversible deterioration in the renal function of susceptible individuals (Ref. 48). Thus, in individuals with decreased renal blood flow, impaired renal function, or hypovolemia, the use of NSAIDs can produce an increase in serum creatinine concentrations and a decrease in creatinine clearance that may progress to acute renal failure, but which is reversible by stopping the drug (Ref. 48). This has necessitated precaution statements in the labeling of prescription NSAIDs directed at the management of patients who use these drugs, despite having prostaglandin-dependent states such as renal disease, heart failure, liver dysfunction, concomitant diuretic therapy, and advanced age that put them at risk for developing this type of nephrotoxicity (Ref. 38). Although the class labeling for prescription NSAIDs also mentions idiosyncratic forms of nephrotoxicity, such as papillary necrosis, acute interstitial nephritis, and nephrotic syndrome that may develop with long-term use of these drugs, these cases are usually not associated with any identifiable risk factor and are rare in occurrence (Ref. 49).

The petition (Ref. 1) included a summary package that was prepared for the August 18, 1983, AAC meeting in which ibuprofen 200 mg was considered for OTC marketing. The summary included safety data generated from clinical trials and supportive evidence from a review of then-published case reports of ibuprofen-associated nephrotoxicity. The summary concluded that although ibuprofen does cause cyclo-oxygenase mediated renal toxicity like other members of the NSAID class, the reversibility of this condition is dependent upon its recognition and the discontinuation of the drug, particularly when it occurs in those at risk, such as the chronically ill or the elderly (Ref. 39).

In support of ibuprofen's renal safety profile, four studies (Refs. 50 through 53) that evaluated the prostaglandin-mediated effects of OTC doses of ibuprofen (≤ 1,200 mg a day) on renal function were reviewed. In a crossover study, Farquhar (Ref. 50) evaluated the renal effects of ibuprofen (1,200 mg daily) and acetaminophen (4 g daily) versus a placebo in 12 healthy men (n = 6) and women (n = 6) who were subjected to progressive renal stress. Subjects were on a low-sodium diet, on limited exercise, and given a drug or placebo for 3 days and the morning of day four. On day four, the participants were subjected to treadmill exercise, in the heat, to cause dehydration. The combined stressors caused decreases in effective renal plasma flow, glomerular filtration rate (GFR), and sodium excretion. Baseline GFR (range 118 to 123 mL/minute (min) decreased to 73 ± 5, 78 ± 4, and 82 ± 5 mL/min, post-exercise, in the ibuprofen, acetaminophen, and placebo groups, respectively, with a significantly greater decrease in GFR for ibuprofen than placebo ($p < 0.05$). The decrease in GFR for the acetaminophen group was not significantly different from placebo. The authors attributed the lower GFR that occurred in the ibuprofen arm of the study to renal prostaglandin inhibition by the drug.

In a randomized, disease-controlled study, Ciabattoni et al. (Ref. 51) evaluated the prostacyclin-mediated effects on GFR and renal blood flow of 20 women with chronic glomerular disease versus 19 normal healthy control subjects following 7 days of treatment with ibuprofen (1,200 mg daily) versus sulindac (400 mg daily). In the 10 subjects with renal insufficiency who were given ibuprofen, the serum creatinine level was increased by about 40 percent and the creatinine and para-aminohippurate clearances were decreased by 28 ± 7 and 35 ± 8 percent, respectively, during treatment ($p < 0.01$). Renal function returned to baseline values after ibuprofen was discontinued, although the serum creatinine and creatinine clearance were still significantly altered up to 5 days after ibuprofen was stopped.

Welton et al. (Ref. 52) evaluated the renal effects of ibuprofen (800 mg three times daily), piroxicam (20 mg daily), and sulindac (200 mg twice daily) in an 11-day, randomized, triple crossover study of 12 women with asymptomatic, mild, stable, chronic renal failure with serum creatinine ranging from 130 to 270 micromoles (μmol)/L. Although all the subjects were able to complete courses of treatment with piroxicam and sulindac, three subjects developed acute decreases in renal function with an elevation in their renal parameters that met the study criteria for stopping (defined as an increase in serum creatinine of 130 μmol/L or more, or a serum potassium value of more than 6 millimole/L (mmol/L)) by the eighth day of treatment with ibuprofen. When these three subjects were rechallenged with ibuprofen, 400 mg three times a day, two again developed acute deterioration of renal function. The authors

concluded that a brief course of nonprescription ibuprofen may result in the precipitous decrease in the renal function of people with asymptomatic, mild, chronic renal failure.

In contrast, Furey et al. (Ref. 53) did a 7-day, double-blind, randomized study comparing the renovascular effects of ibuprofen (400 mg three times daily) versus that of aspirin (650 mg three times daily) and acetaminophen (650 mg three times daily) in 25 elderly subjects with mild renal insufficiency, and hypertension controlled with thiazide diuretics. Although the mean baseline serum creatinine levels for all three treatment groups were comparable, the mean baseline serum creatinine clearances were higher in both the acetaminophen (78.9 ± 8.3 mL/min) and aspirin (67.1 ± 6.4 mL/min) treatment groups as compared to the ibuprofen group (56.3 ± 5.3 mL/min). On analysis, this was not found to be statistically different. This study failed to demonstrate any statistically significant changes in the five renal parameters (serum creatinine, creatinine clearance, blood urea nitrogen (BUN), serum potassium and sodium) evaluated in any of the three treatment groups.

The three studies by Farquhar (Ref. 50), Ciabattoni et al. (Ref. 51), and Welton et al. (Ref. 52) demonstrated that, at an OTC dose of ibuprofen (1,200 mg daily), hemodynamic changes in the kidney do occur in subjects with prostaglandin-dependent states, which can lead to diminished renal function. The inability of the study by Furey et al. (Ref. 53) to demonstrate any significant deterioration in any of the renal parameters studied may be due to the fact that the subjects who participated in this study may not have had severe enough renal disease as manifested by the mildly elevated range of their baseline mean serum creatinine from 1.4 ± 0.08 mg/deciliter (dL) to 1.5 ± 0.07 mg/dL to demonstrate ibuprofen's prostaglandin-dependent renal effects. Thus, despite their histories of hypertension and the concomitant use of diuretics, these subjects may also have had adequate renal reserves to compensate for any ibuprofen-mediated decreases in their renal function.

The largest study involving an OTC dose of ibuprofen that included monitoring of renal function was the 4-week study by Bradley et al. (Ref. 42). This study compared the effectiveness of low-dose (1,200 mg daily) and high-dose (2,400 mg daily) ibuprofen and acetaminophen (4,000 mg daily) in the treatment of osteoarthritis in 184 subjects. Side effects were similar in all three groups. The serum creatinine level increased by more than 17 μmol/L (0.2 mg/dL) in four of the subjects receiving low-dose ibuprofen, six receiving high-dose ibuprofen, and one receiving acetaminophen. As a group, the serum creatinine concentration increased only slightly (2.7 μmol/L) in the high-dose ibuprofen group ($p = 0.04$), but there was no increase in the low-dose group. Although this trial is the only study which compared a low-dose (i.e., OTC dose) to a high-dose (i.e., prescription-strength dose) ibuprofen and could possibly be interpreted as a dose-ranging study for the renal effects of ibuprofen-mediated prostaglandin inhibition, the subjects who were entered into this trial were healthy with a mean age of 55.7 ± 13.7 to 57.2 ± 11.7 years. Exclusion criteria prohibited participation by subjects with medical conditions that contraindicated the use of the study medications. Thus, the study subjects were not reflective of the population identified at risk for developing this type of nephrotoxicity.

The petition included numerous case reports (Refs. 54 through 61) of renal failure associated with the use of OTC doses of ibuprofen in people with normal renal function. Four cases (Refs. 54 through 57) described the syndrome of acute flank pain with reversible renal failure following short-term doses of 1,200 mg, or less, of ibuprofen. One (Ref. 54) of these four cases was confounded by the concomitant use of alcohol, and one (Ref. 55) used alcohol and acetaminophen, both of which can cause nephrotoxicity. Four reports (Ref. 58 through 61) described cases of idiosyncratic drug-induced types of renal failure. One of the cases (Ref. 61) discussed a case of idiosyncratic hypersensitivity reaction in an elderly man who experienced acute renal failure twice; once after taking ibuprofen orally and, again, a few years later, after using a topical formulation of ibuprofen. Renal function returned to normal in all eight people after medical therapy. The agency is aware of additional case reports of patients who developed renal toxicity after taking ibuprofen (Refs. 62 through 66).

In 1996, the National Kidney Foundation published a position paper in which it recommended that consumer labeling of OTC analgesic drug products contain warnings directed to the population at risk for the development of nephrotoxicity associated with the use of these products (Ref. 67). These recommendations were based on the review of a database that contained 556 articles on aspirin, acetaminophen, aspirin/acetaminophen combinations, and NSAID-related renal disease by an ad hoc group of expert investigators and clinicians. This committee suggested the following consumer warning for OTC NSAID-containing products:

> DO NOT TAKE THIS PRODUCT WITHOUT PHYSICIAN SUPERVISION IF: (1) You are allergic to aspirin; (2) you are under a physician's care for asthma or stomach problems (such as heartburn); (3) you take diuretic medicine; (4) you have heart disease, high blood pressure, kidney disease, or liver disease; (5) you are over 65 years of age.

The information contained in the literature review and case reports submitted in support of this petition confirms that OTC doses of ibuprofen can exert a variety of renal adverse effects, particularly in those who are predisposed by prostaglandin-dependent states. Although the sporadic nature of the idiosyncratic drug-induced type of ibuprofen nephrotoxicity makes it impossible to predict which group of individuals is at risk for developing this type of adverse event, this is not the case with individuals who experience prostaglandin-driven hemodynamic changes in renal function. The latter, if recognized, is reversible following discontinuation of the drug. Thus, based on the information reviewed, the agency concurs with the recommendations made by the National Kidney Foundation that the consumer labeling for OTC ibuprofen should have a warning directed at those at risk for the development of acute renal failure associated with the use of the product. The agency is proposing a warning that includes: ''Ask a doctor before use if you have: • high blood pressure, heart or kidney disease, are taking a diuretic, or are over 65 years of age''.

c. *Hepatic.* The petition (Ref. 1) contained only one case report (Ref. 68) from the literature of biopsy-proven drug-induced hepatitis that occurred in a person taking 1,200 mg daily ibuprofen and cefadrine. The authors concluded that the liver lesion was induced by drug hypersensitivity. The supplemental submission (Ref. 10) included one case report (Ref. 69) of drug-induced vanishing bile duct syndrome secondary to ibuprofen. Similarly, the authors of this report concluded that the reaction was induced by a drug hypersensitivity.

In a retrospective, crossover cohort study, Garcia-Rodriguez et al. (Ref. 70) evaluated the risk of developing serious, acute, noninfectious liver injury associated with the use of NSAIDs. One of the 16 subjects was identified as having NSAID-induced hepatitis: A 93-year-old male who developed cholestatic jaundice after taking 1,200

mg of ibuprofen along with other hepatotoxic drugs. Causality could not be directly associated with ibuprofen in this case due to the concomitant use of other hepatotoxic drugs.

In a review of FDA postmarketing data of NSAID-induced hepatotoxicity, Katz et al. (Ref. 71) noted that while ibuprofen is known to cause idiosyncratic metabolic toxicity of the liver, ibuprofen and ketoprofen were found to have the lowest reported calculated incidences of hepatotoxicity (0.55 percent and 0.56 percent respectively) of all NSAIDs evaluated at that time. Due to the limitations of FDA's reporting requirements, the authors were unable to estimate separately the incidence of this phenomena associated with OTC doses of ibuprofen. Given the available information, the agency sees no need to propose a hepatitis warning at this time.

d. *Blood*. Three case reports from the literature described hematological events attributed to ibuprofen (Refs. 72, 73, and 74). Two of these (Refs. 72 and 73) involved individuals taking OTC doses of ibuprofen who developed thrombocytopenia and white-cell aplasia with bone marrow plasmacytosis. The duration of ibuprofen use was not stated in the second case report. The third individual (Ref. 74), taking an undisclosed dose of ibuprofen (by prescription), developed Pelger-Huet syndrome due to a complement-dependent immunoglobulin G (IgG) antibody that prevented bone marrow production of myeloid stem cells. Ibuprofen is known to reversibly inhibit platelet aggregation (Ref. 75). Further, ibuprofen has been shown to potentiate the effects of warfarin. As a result, the agency believes consumers who are taking anticoagulants should be alerted to check with a health professional before taking ibuprofen because of the potential for bleeding. Thus, the agency is proposing a warning that includes: ''Ask a doctor or pharmacist before use if you are: • taking a prescription drug for anticoagulation (blood thinning)''.

e. *Immune system*. Ibuprofen has been associated with some hypersensitivity reactions. The petition (Ref. 1) included 14 case reports (Refs. 76 through 86) from the worldwide literature that described hypersensitivity and anaphylactic reactions to ibuprofen. The reports of ibuprofen-associated hypersensitivity (Refs. 76 through 80) included six individuals with underlying histories of asthma (one (Ref. 78) of whom also had a known allergy to aspirin). Three of the individuals with asthma died following hypersensitivity reactions that were attributed to ibuprofen (Refs. 76, 77, and 78). One report (Ref. 86) included five patients with Sjögren's syndrome who developed symptomatic drug allergies after taking ibuprofen.

Hypersensitivity reactions were also reported in one individual (Ref. 80) with general allergies (including a known aspirin sensitivity), in one individual (Ref. 82) with systemic lupus erythematosus, and in three individuals (Refs. 83, 84, and 85) with no apparent underlying illnesses (one (Ref. 84) had taken aspirin just prior to the reaction). The petition also included an abstract of a report of challenge testing with ibuprofen (Ref. 87) in 42 people with histories of allergies to various analgesic agents. Five people experienced anaphylactic reactions to incremental doses of up to 500 mg of ibuprofen. Eleven of 33 subjects had similar reactions to aspirin. The agency is proposing an ''Allergy alert'' warning and additional allergy warning statements for all OTC drug products containing NSAID IAAA active ingredients. (See section IV of this document.)

f. *Nervous system*. The petition (Ref. 1) included 20 literature citations (Refs. 82 and 88 through 106) that described 21 individuals with aseptic meningitis associated with the use of ibuprofen. Twelve of these individuals (Refs. 82, 88 through 95, 98, and 100) had underlying histories of systemic lupus erythematosus or other immune disorders, 3 (Ref. 96) had histories of arthritis, 1 (Ref. 97) had a history of spontaneous recurrent aseptic meningitis, and 5 (Refs. 100 through 104) reportedly had no underlying medical problems. The supplemental submission (Ref. 10) included several review articles (Refs. 107 through 110) that described the spectrum of central nervous system side effects reported to be associated with NSAIDs, as well as case reports (Refs. 111 through 115) of aseptic meningitis associated with the use of a variety of NSAIDs. Although there has been an increase in availability and use of NSAIDs in general, the overall number of aseptic meningitis cases reported to be associated with the use of these agents since 1978 is only about 35. Most of the case reports (Refs. 111, 112, and 114) involved individuals with underlying collagen vascular disorders (i.e., systemic lupus erythematosus and rheumatoid arthritis). Several cases (Refs. 111, 113, and 115) established direct causality by histories of positive dechallenge-rechallenge with the suspected NSAID. While other NSAIDs were sometimes implicated, ibuprofen was the most commonly reported. The agency does not believe a nervous system warning is needed at this time.

g. *Skin*. There were a total of seven case reports (Refs. 116 through 122) and two articles (Refs. 123 and 124) on the results of provocative skin testing with ibuprofen. The seven case reports describe episodes of fixed drug reactions (Ref. 116), erythema nodosum (Ref. 117), a bullous drug eruption (Ref. 118), various cases of urticaria (Ref. 119), exacerbations of psoriasis (Refs. 120 and 121), and the occurrence of dermatitis herpetiformis (Ref. 122). The doses of ibuprofen involved in these cases, when reported, were 800 mg daily. The two articles (Refs. 123 and 124) described the results of provocative testing with a variety of drugs including ibuprofen. Of the 169 patients tested, 11 had positive skin reactions to ibuprofen. As stated above, the agency is proposing allergy warnings for OTC drug products containing NSAIDs. (See section IV of this document.)

h. *Special senses*. There were three case reports (Refs. 125, 126, and 127) and one adverse event, which occurred during a clinical trial (Ref. 128), that mentioned ibuprofen's effects on the visual parameters. The reports involved macular hemorrhage in people with age-related maculopathy (Ref. 126), vortex keratopathy (Ref. 127), iridocyclitis (Ref. 125), and depressed contrast sensitivity (Ref. 128) associated with total daily doses of ibuprofen ranging from 800 to 2,400 mg. Given the available information, the agency sees no need to propose a special senses warning at this time.

3. Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) Data

The petition analyzed adverse event data from the FDA SRS for all single-ingredient OTC ibuprofen drug products marketed in the United States for the time period from May 1984 through July 1996. Adverse reaction reports associated with a generic OTC ibuprofen drug product marketed under an ANDA or prescription ibuprofen drug products used at OTC doses were excluded from this analysis. A total of 8,168 case reports associated with 16,627 adverse events in the SRS database attributed to the use of single-ingredient, nongeneric OTC ibuprofen were thus identified. The total number of adverse events was greater than the total number of case reports because some case reports included more than one adverse reaction associated with the use of the drug.

The petitioner screened the electronic records of all case reports for confounding factors. Reports were

considered confounded if they included the coadministration of at least one other medication (drug confounder), the administration of ibuprofen in a dose greater than 1,200 mg/day (dose confounder), the administration of ibuprofen for more than 10 days (duration confounder), or if the subject was less than 12 years of age (age confounder). Reports with missing or unreliable data were included in the analysis. Screening for confounders yielded 3,540 nonconfounded case reports which generated 6,197 adverse events. Case reports were then reviewed to identify serious reports associated with OTC ibuprofen. Of the 3,540 nonconfounded case reports, 592 were considered to be serious in nature. FDA's definition of a serious outcome is an event that results in death or hospitalization, is life threatening, produces permanently disability or congenital anomaly, or one in which medical intervention is required. However, the case report forms for these serious reactions were not included in the petition. The petition (Ref. 1) submitted information on case reports from the SRS associated with the use of OTC ibuprofen, reported by COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) body system terminology. The information is summarized in table 1 of this document and represents the number of case reports that included at least one adverse event associated with the COSTART term.

TABLE 1.—SUMMARY OF CASES ASSOCIATED WITH THE USE OF OTC IBUPROFEN IN THE FDA SPONTANEOUS REPORTING SYSTEM FROM MAY 1984 THROUGH JULY 1996 (REF. 1)

COSTART Term	No. of Cases Reported	No. of Nonconfounded Cases	No. of Serious Nonconfounded Cases
Allergic reaction/ anaphylaxis	461	261	72
Body as a whole	3,686	1,786	236
Cardiovascular system	795	293	127
Digestive system	2,445	916	236
Endocrine system	32	12	8
Hematological/lymphatic systems (blood)	679	141	92
Liver	165	35	9
Metabolic and nutritional system	757	176	71
Musculoskeletal system	163	49	7
Nervous system	1,447	577	101
Respiratory system	629	250	81
Skin and appendages	1,339	589	71
Special senses	479	188	29
Urogenital system	716	176	61

The 592 serious nonconfounded case reports included 7 deaths associated with the use of OTC ibuprofen (2 GI, 1 hematological effects, 2 anaphylaxis, 1 miscarriage, and 1 in utero exposure resulting in the postpartum death of an encephalic infant). As shown above in table 1 of this document, the largest number of adverse events involved the GI system. Of the 236 nonconfounded serious case reports related to the GI system, 94 were GI hemorrhage, 52 were various ulcerations, 32 were melena, 25 were abdominal pain, and 20 were hematemesis. This additional evidence supports the need for a GI tract warning in the consumer labeling of OTC ibuprofen drug products.

FDA queried its AERS database for reports of renal failure in adults, over 16 years of age, associated with the use of OTC doses of ibuprofen for the period extending from the time of initial approval for OTC marketing (May 18, 1984) through August 10, 1999 (Ref. 129). For completeness, a search of the AERS database was also done for reports of renal failure in people 16 years of age and under. Fourteen cases of renal failure were identified in this population. In 8 of the 14 cases, a children's suspension formulation was used while, in the remaining 6 cases, 200-mg tablets were reportedly ingested. After excluding cases involving prescription dosages, overdoses, or duplication, there were a total of 80 cases of renal failure in adults over 16 years of age associated with the use of 1,200 mg, or less, of ibuprofen a day. Although 37 of these 80 cases had positive dechallenges with the discontinuation of ibuprofen (which is supportive of the reversibility of this drug-induced adverse event), 9 cases required dialysis treatment. Of these 80 cases, 56 were severe enough to require hospitalization, with 9 reported deaths, out of which 5 listed ibuprofen-induced renal failure as a contributing cause of death. Hypertension (16), pre-existing renal insufficiency (8), diabetes (7), other cardiac problems (8), alcoholism (3), and hepatic disease (2) were some of the most commonly concurrent medical disorders reported. In addition, 15 people were reported to have been taking diuretics prior to developing renal failure. These cases further support the need for consumer labeling directed at those individuals with predisposing medical conditions for the development of ibuprofen-induced prostaglandin-dependent renal toxicity. (See section III.B.2.b of this document.)

4. American Association of Poison Control Center (AAPCC) Data

The petition (Ref. 1) also included data on ibuprofen from the Toxic Exposure Surveillance System (TESS) collected by the AAPCC from 1987 to 1996. During that time, TESS reported only 9 fatalities from 163,948 OTC ibuprofen exposures compared to 450 fatalities from 312,618 acetaminophen exposures, and 401 fatalities from 153,495 aspirin exposures. The supplemental submission (Ref. 10) included additional information on the nine deaths, reports of seven additional deaths related to OTC ibuprofen in 1997, and three other deaths related to OTC or prescription-strength ibuprofen that occurred in 1996.

Of these 19 deaths, 14 were classified as intentional suicides. One person ingested 165 tablets of 200-mg strength ibuprofen and the other 13 ingested other drugs in combination with OTC ibuprofen. Of the remaining five cases, one was classified as a therapeutic error in a person with a history of alcoholism and hepatic disease waiting for a liver transplant, who reportedly took ''excessive'' amounts of acetaminophen and ibuprofen for pain. This person's death was attributed to chronic hepatic failure associated with ethanol and

acetaminophen toxicity, chronic pancreatitis, and gastritis.

Another case was reported as intentional misuse in a patient with a history of chronic alcoholism, cirrhosis, and portal hypertension who developed acute liver failure following the chronic use of ibuprofen and acetaminophen. Another case of reported intentional misuse involved a patient with a history of drug abuse who reportedly ingested 27 tablets containing 100 mg propoxyphene napsylate and 650 mg acetaminophen and 50 tablets of ibuprofen (strength not specified) over a 16- to 48-hour period. The remaining two cases were listed as adverse drug reactions in young children. Thus, a large majority of the deaths were suicidal overdoses or intentional abuse associated with the concomitant use of other drugs, and should not be directly attributed to ibuprofen. A few of the cases could have been due to allergic reactions related to ibuprofen use. An allergy warning is required to appear in the labeling of OTC ibuprofen drug products marketed under an NDA/ANDA to alert consumers of that risk.

5. Drug-Drug Interactions

The petition (Ref. 1) included eight journal articles (Refs. 53 and 130 through 135) that described clinical trials involving a variety of antihypertensive agents (i.e., calcium channel blockers, angiotensin converting enzyme inhibitors, and triamterene-hydrochlorothiazide) in chronically treated and elderly hypertensive patients with renal insufficiency who took OTC doses of ibuprofen. The studies did not demonstrate any diminished antihypertensive effectiveness when these drugs were coadministered with ibuprofen. This is in contrast to the diminution in the effectiveness of a variety of antihypertensive medications such as beta-blockers, ACE inhibitors, hydralazine, and diuretic agents in patients who use prescription doses of NSAIDs (Ref. 136).

6. Tentative Conclusion on the Safety of Ibuprofen

Based on the evaluation of available information, the agency concludes ibuprofen is generally recognized as safe for OTC use by adults and children 12 years of age and older, if the labeling includes appropriate warnings and directions for use. The agency is proposing to include warnings to alert individuals of the potential for renal and GI problems associated with the use of ibuprofen. For consistency in labeling, the agency is also proposing to include the same allergy alert warning statements in the labeling of all OTC NSAID products.

C. Effectiveness

The reports of clinical effectiveness trials submitted in the petition (Ref. 1) compared OTC doses of ibuprofen to aspirin, acetaminophen, and/or codeine-containing analgesic compounds. The petition identified a number of double-blind, randomized clinical trials, either placebo or active controlled. Most of the studies are generally applicable to the indications proposed in § 343.50 of the TFM for other OTC internal analgesic/antipyretic drug products (e.g., dental pain, pain of arthritis, dysmenorrhea, headache, and sore throat). Nineteen studies (Refs. 137 through 155) were placebo-controlled, and the reports concluded that ibuprofen, at the OTC doses studied, was a more effective analgesic agent than placebo. The authors of these studies (Refs. 137 through 155) and three active-controlled trials (Refs. 156, 157, and 158) also reported that, at the OTC doses studied, ibuprofen was either comparable to or more effective than aspirin, acetaminophen, and various strengths of codeine-containing analgesics or other NSAIDs tested. The pain models included in the studies were dental, headache, episiotomy, sore throat, and dysmenorrhea. One report (Ref. 159) described the results of two randomized, double-blind, parallel studies that compared the antipyretic effectiveness of ibuprofen to aspirin in adults, which showed effectiveness of both the 200- and 400-mg doses of ibuprofen.

The only dosage forms used in the trials and identified in the reports were tablets, caplets, and capsules. Some of the reports did not identify the dosage form. Table 2 of this document summarizes the placebo-controlled and active-controlled trials the agency reviewed to demonstrate the effectiveness of OTC doses of ibuprofen for various pain and fever models.

TABLE 2.—TRIALS TO DEMONSTRATE THE EFFECTIVENESS OF IBUPROFEN FOR VARIOUS PAIN AND FEVER MODELS

Investigator(s) (reference number)	Type of Pain Measured	Dosage Form	Treatment[2] (dosage in mg)	Reported Results
Cooper (137)	Dental	Tablets	I 400; AP 600; AP300 + C 30; AP 600 + C 60; P	I more effective than AP 600, AP 300 + C 30, and P (p values not given)
Cooper (138)	Dental	Tablets	I 400; C 60; A 650; A 650 + C 60; I 400 + C 60; P	I 400 more effective than A ($p<0.05$) and C ($p<0.001$); I + C more effective than A + C ($p<0.05$)
Cooper (139)	Dental	N.S.[1]	I 200; AP 650; P	I more effective than P ($p<0.05$); I comparable to AP
Cooper (140)	Dental	N.S.[1]	I 200; I 400; AP 1000; P	I 200 and I 400 comparable to AP; all more effective than P (p values not given)
Cooper (141)	Dental	N.S.[1]	I 200; I 400; AP 1000; P	I 200 and I 400 comparable to AP; all more effective than P (p values not given)
Cooper (142)	Dental	N.S.[1]	I 200; AP 650; I 200 + AP 650; P	I more effective than AP ($p<0.05$) and P ($p<0.025$); I + AP more effective than AP ($p<0.05$) and P (p value not given)
Cooper et al. (143)	Dental	N.S.[1]	I 400; AP 1000; P	I more effective than AP ($p<0.05$) and P ($p<0.001$)
Forbes et al. (144)	Dental	Capsule	I 400; AP 600; AP 600 + C 60; K 10; K 20; P	I, K 10 and K 20 not significantly different; I more effective ($p<0.05$) than AP and AP + C; all more effective than P ($p<0.01$)

TABLE 2.—TRIALS TO DEMONSTRATE THE EFFECTIVENESS OF IBUPROFEN FOR VARIOUS PAIN AND FEVER MODELS—Continued

Investigator(s) (reference number)	Type of Pain Measured	Dosage Form	Treatment[2] (dosage in mg)	Reported Results
Forbes et al. (145)	Dental	Capsule	I 400; A 650; B 5; B 10; B 25; P	I more effective (p<0.01) than A, B 5, and B 10; I comparable to B 25; all more effective than P (p<0.01 to p<0.05)
Forbes et al. (146)	Dental	Capsule	I 400; A 650; B 10; B 25; B 50; B 100; P	I more effective than A (p<0.01); B 25 and B 100 more effective than I (p<0.01); all more effective than P (p<0.01)
Giles et al. (147)	Dental	N.S.[1]	1 200; C 15; I 200 + C 15; A 600; P	I comparable to A and I + C, and more effective (p<0.05) than C and P; I + C comparable to A and more effective (p<0.05) than C and P
Jain et al. (148)	Dental	Tablet	I 100; I 200; I 400; A 650; P	I (all doses) and A more effective than P (p<0.001); no consistent significant difference among active groups
Mehlisch et al. (149)	Dental	Tablet or caplet	I 400; AP 1000; P	I more effective (p<0.001) than AP and P; AP more effective than P (p<0.001)
Ngan et al. (150)	Dental	Capsule	I 400; A 650; P	I more effective (p<0.05) than A and P; A more effective than P (p<0.05)
Diamond (151)	Headache	Tablet	I 400; I 800; A 650; P	No statistically significant difference among active drugs; all active drugs more effective than P (p = 0.02 to p = 0.018)
Schachtel et al. (152)	Headache	Capsule	I 400; AP 1000; P	I more effective (p<0.01) than AP and P; AP more effective than P (p<0.01)
Nebe et al. (153)	Headache	Tablet	I 200; A 500; P	I at least as effective as A; I and A more effective than P (p = 0.002 and 0.046, respectively)
Schachtel et al. (154)	Episiotomy	N.S.[1]	I 400; AP 1000; P	I more effective (p<0.05) than AP and P; AP more effective than P (p<0.05)
Schachtel et al. (155)	Sore throat	N.S.[1]	I 400; AP 1000; P	I more effective (p<0.01) than AP and P; AP more effective than P (p<0.01)
Habib et al. (156)	Dental	Enteric coated tablets.	I 400; DHC 30; A 600 + CA 60 (soluble); AP 1000 + C 16 + CA 60 (dispersible)	I comparable to AP + C + CA (p>0.05) and A + CA (p>0.05); All more effective than DHC (p<0.001 in each case)
Noyelle et al. (157)	Headache	Capsule	I 400; A 650; A 1000; AP 1000	I comparable to A 1000; I more effective (p>0.01) than A 650 and AP 1000
Milsom and Andersch (158).	Dysmenorrhea	N.S.[1]	I 400; N 250; AP 500	I reduced pain (p<0.05); I more effective than N and AP (no p value given); N and AP no significant reduction in pain
Gaitonde et al. (159)	Fever	Capsule	I 200; A 300 (Study 1), I 400; A 600 (Study 2)	I 200 and I 400 effective as antipyretics; I 200 comparable to A 300 (p>0.05); I 400 comparable to A 600 (p>0.05)

[1] N.S. = Not stated.
[2] A = aspirin; AP = acetaminophen; B = bromfenac; CA = caffeine; C = codeine; DHC = dihydrocodeine; I = ibuprofen; K = ketorolac; N = naproxen sodium; P = placebo.

The agency has evaluated the reports and agrees that the studies support the effectiveness of ibuprofen as an OTC drug product for a variety of pain and fever models. These studies support the general recognition of racemic ibuprofen as an effective internal analgesic/antipyretic drug at a minimum dose of 200 mg every 4 to 6 hours.

D. Labeling

Internal analgesic/antipyretic drug products containing ibuprofen have been marketed for OTC use under the NDA/ANDA process for many years with indications for use and warnings similar to those proposed in § 343.50(b) and (c) of the TFM for other OTC internal analgesic/antipyretic drug products. In the **Federal Register** of March 17, 1999 (64 FR 13254), FDA established a standardized format and standardized content for the labeling of OTC drug products (§ 201.66 (21 CFR 201.66)). Table 3 of this document shows parts of the approved labeling for currently marketed OTC ibuprofen drug products for adults under the NDA process, using the new ''Drug Facts'' labeling format in § 201.66.

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Table 3.--Current (NDA) Ibuprofen Labeling using the Format in § 201.66

Drug Facts

Active Ingredient (in each tablet)	***Purpose***
Ibuprofen (200 mg)	Pain reliever/fever reducer

Uses

- temporarily relieves minor aches and pains due to:
  - minor pain of arthritis
  - headache
  - backache
  - menstrual cramps
  - the common cold
  - muscular aches
  - toothache
- temporarily reduces fever

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling
- asthma (wheezing)
- shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do not use if you have ever had an allergic reaction to any other pain reliever/fever reducer

Ask a doctor before use if you have:

- stomach pain
- problems or serious side effects from taking pain relievers or fever reducers

Ask a doctor or pharmacist before use if you are:

- under a doctor's care for any serious condition
- taking any other drug
- taking any other product that contains ibuprofen or any other pain reliever/fever reducer

When using this product take with food or milk if stomach upset occurs

Stop use and ask a doctor if:

- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms occur

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults:
  - take 1 tablet every 4 to 6 hours while symptoms persist
  - if pain or fever does not respond to 1 tablet, 2 tablets may be used
  - do not exceed 6 tablets in 24 hours unless directed by a doctor
  - the smallest effective dose should be used
- children under 12 years: ask a doctor

Other information ■ store at 20 - 25°C (68 - 77°F). ■ avoid high humidity and excessive heat above 40°C (104°F).

Inactive ingredients *[list inactive ingredients in alphabetical order]*

Questions or Comments? Call xxx xxx xxxx

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In addition to the indications approved for currently marketed OTC ibuprofen 200-mg products, the proposed labeling in the TFM for other internal analgesic/antipyretic drug products includes an indication for sore throat in § 343.50(b)(1). The agency will discuss the proposed sore throat indication for all of these drug products in a future issue of the **Federal Register**. Currently marketed ibuprofen for adult use does not include an indication for sore throat. Thus, the agency is not including a sore throat claim for ibuprofen in this current proposal.

The approved labeling of OTC drug products containing aspirin, ibuprofen, ketoprofen, and naproxen sodium as active ingredients, marketed under the NDA/ANDA process, includes an ''Allergy alert'' warning and additional allergy warning statements under the headings ''Do not use'' and ''Stop use and ask a doctor if'' (see table 3 of this document). These allergy warning statements are similar to the allergy warnings requested in the petition. Proposed labeling for OTC drug products containing aspirin ingredients in § 343.10(b) and (c) (21 CFR 343.10(b) and (c)) of the TFM also includes an allergy warning in § 343.50(c)(1)(iv), which states: ''Do not take this product if you are allergic to aspirin or if you have asthma unless directed by a doctor.'' For those products containing salicylate active ingredients in § 343.10(d) through (f) the proposed warning in § 343.50(c)(1)(vi) of the TFM states: ''Do not take this product if you are allergic to salicylates (including aspirin) unless directed by a doctor.''

The Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (the Panel) proposed allergy warnings for aspirin. In discussing the safety of OTC aspirin use (42 FR 35346 at 35397 through 35399, July 8, 1977), the Panel concluded that in sensitive individuals aspirin produces allergic type reactions, that include: (1) Rash, (2) swelling, (3) hives and giant hives, (4) shortness of breath to severe asthma attacks, and (5) anaphylactic shock involving laryngeal swelling and a precipitous drop in blood pressure. The Panel provided a detailed discussion of the importance of an aspirin hypersensitivity warning (42 FR 35346 at 35397). The Panel noted that the incidence of hypersensitivity reactions (dermal and pulmonary) has been estimated to be about 0.2 percent of the general population, but that as much as 20 percent is found in some subgroups (asthmatics and people with chronic urticaria). Thus, the Panel concluded that these adverse effects occur in a significant proportion of the population and they can be serious and even life-threatening in some instances.

The Panel suggested an asthmatic response to aspirin is nonimmunologic and related to the inhibition of prostaglandin synthesis, and noted that cross-sensitivity is commonly seen with other prostaglandin synthesis inhibitors including indomethacin, flufenamic acid, mefenamic acid, ibruprofen, and phenylbutazone. The Panel suggested dermal hypersensitivity is an immunologic response, and that these individuals also appear to be susceptible to anaphylaxis and more susceptible to cross-sensitivity to salicylic acid and acetaminophen (42 FR 35346 at 35398). The Panel concluded, based on the known risk of aspirin and salicylate hypersensitivity in a significant portion of the general population, that these products should bear warnings alerting consumers who are allergic to these products to consult a doctor before using the products (42 FR 35346 at 35499). The agency has determined that a consistent approach is needed for all OTC NSAID drug products. As discussed in section IV of this document, the agency is proposing standardized allergy alert and warning statements for all OTC NSAID IAAA drug products.

In the safety discussion above (sections III.B.2.a, III.B.2.b, III.B.2.d, and III.B.3), the agency noted that the use of ibuprofen has some risk for certain individuals. GI bleeding may be increased for certain at-risk individuals (i.e., people with ulcers). For people taking anticoagulants, the risk for GI bleeding is already increased, and the use of ibuprofen by those individuals is likely to further increase that risk. Individuals with certain medical conditions are at increased risk for developing renal failure. The agency believes individuals need to be alerted to these risks. The agency is proposing that the labeling of ibuprofen include warnings related to GI bleeding, use of anticoagulant drugs, and medical conditions that predispose individuals to renal failure, using the standardized labeling format for OTC drug products.

IV. The Agency's Tentative Conclusions and Proposals

After reviewing the information submitted and other relevant information, FDA has determined that ibuprofen 200-mg tablets have been used for a material time and to a material extent to qualify for inclusion in an OTC drug monograph. Therefore, FDA is proposing that ibuprofen, in 200-mg tablet formulation, be generally recognized as safe and effective as an OTC IAAA drug for adults and children 12 years of age and older. The safety and effectiveness of ibuprofen are further supported by the data the agency evaluated in two NDAs in 1983, the findings of the AAC in 1983, and the subsequent marketing history of ibuprofen for OTC use. The agency believes ibuprofen can be marketed OTC under the monograph system for the indications previously approved under the NDA/ANDA process for adult formulations if labeled with the appropriate warnings and directions for use. The agency agrees with the petition that the proposed labeling should only include adults and children 12 years of age and older. The agency is proposing to amend the TFM for OTC IAAA drug products to include ibuprofen 200 mg, in tablet formulation, in § 343.10(g) as a safe and effective ingredient for the relief of pain and fever in adults and children 12 years of age and older, and to include specific warnings and directions for use in § 343.50(c) and (d), similar to those suggested by the petition and those approved by FDA for currently marketed OTC ibuprofen drug products under the new drug review process. The proposed labeling is in a different format than that requested by the petition. However, the format is consistent with the new OTC labeling format in § 201.66, which was issued after the petition was submitted. In addition to the warnings already included in the labeling for OTC ibuprofen drug products under the NDA/ANDA process, the agency is proposing warning statements related to GI and renal problems and use of anticoagulant drugs.

The agency also tentatively concludes that, for consistency, the ''Allergy alert'' and additional allergy warning statements required for ibuprofen, ketoprofen, and naproxen sodium should be extended to all OTC NSAID IAAA drug products, whether marketed under an OTC drug monograph or an NDA/ANDA. These standardized allergy alert and warning statements (in proposed § 201.324) would provide the following information:

(a) Allergy alert: [insert name of active ingredient (first letter of first word for ingredient in uppercase)] may cause a severe allergic reaction which may include: • hives • facial swelling • asthma (wheezing) • shock

(b) Do not use: • if you have ever had an allergic reaction to any other pain reliever/fever reducer [This statement appears as the first warning under the subheading ''Do not use.'']

(c) Stop use and ask a doctor if: • an allergic reaction occurs. Seek medical help right away. [These statements appear as the first warning under the subheading ''Stop use and ask a doctor if.'']

Should this proposed amendment to part 201 relating to allergy warning statements for OTC IAAA drug products be published as a final rule, then the proposed allergy warnings in §§ 343.50(c)(1)(iv)(A), (c)(1)(vi), (c)(2)(iv)(A), and (c)(2)(vi) will be replaced with a reference to the allergy warning requirements in proposed § 201.324. Final agency action on this proposal will occur in a future issue of the **Federal Register**.

V. Summary of Proposed Agency Changes

Section 201.63

1. The agency is proposing to amend the third-trimester pregnancy warning to include OTC drug products containing ibuprofen.

Section 201.324 (proposed)

2. The agency is proposing to require an ''Allergy alert'' and additional allergy warning statements for all OTC drug products containing NSAID IAAA active ingredients—including, but not limited to, aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate. (See section III of this document.)

Part 343 (21 CFR Part 343)

3. The agency is proposing to add a definition for ibuprofen in § 343.3.

4. The agency is proposing to add § 343.10(g) to include ibuprofen as an active ingredient.

5. The agency is proposing to reword the statements in § 343.20(b)(2) providing for the combination of any analgesic/antipyretic in § 343.10 and cough-cold products and in § 343.20(b)(4) providing for the combination of any analgesic in § 343.10 and diuretic drug products to provide for combinations with specific IAAA active ingredients (but not including ibuprofen). The petition did not include data for the safety and effectiveness of ibuprofen in combination with these ingredients, nor did it request ibuprofen, as a combination drug product, to be included in the TFM.

6. The agency is proposing to revise the headings in proposed § 343.50(b)(1), (c)(1)(i), and (c)(2)(i) from ''For products containing any ingredient in § 343.10.'' to ''For products containing any ingredient in § 343.10(a) through (f)'' to limit those paragraphs to specific active ingredients (not including ibuprofen).

7. The agency is proposing to add § 343.50(b)(5) to include indications for ibuprofen.

8. The agency is proposing to revise the phrase related to allergy in the allergy/asthma warning for adults in proposed § 343.50(c)(1)(iv)(A) to read as follows: ''Do not use this product if you have asthma unless directed by a doctor''. Similarly, for products labeled for children in § 343.50(c)(2)(iv)(A) the agency is proposing to revise the warning to read as follows: ''Do not give this product to children who have asthma unless directed by a doctor''.

9. The agency is proposing to revise the warning in proposed § 343.50(c)(1)(iv)(B) to reference the pregnancy/breast-feeding warnings in § 201.63(a) and (e).

10. The agency is proposing to revise the warnings in § 343.50(c)(1)(iv)(A), (c)(1)(vi), (c)(2)(iv)(A), and (c)(2)(vi) for adults and children, respectively, to require the allergy warning statements in proposed § 201.324 for products containing any ingredient in § 343.10(b) through (g). (The allergy part of the previously proposed allergy/asthma warning in § 343.50(c)(1)(iv)(A) is now covered by proposed § 201.324.)

11. The agency is proposing the following warnings for drug products containing ibuprofen in § 343.10(g) labeled for use by adults:

(a) The ''Allergy alert'' warnings in proposed § 201.324(a), (b), and (c).

(b) The alcohol warning in § 201.322(a)(2).

(c) The following statements after the subheading ''Ask a doctor before use if you have:

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

(d) The following statements after the subheading ''Ask a doctor or pharmacist before use if you are:

- under a doctor's care for a serious condition
- taking any other product that contains ibuprofen, or any other pain reliever/fever reducer
- taking a prescription drug for anticoagulation (blood thinning)
- taking any other drug''.

(e) The following statement after the subheading ''When using this product take with food or milk if stomach upset occurs''.

(f) The following statements after the subheading ''Stop use and ask a doctor if:

- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear''.

(g) The pregnancy/breast-feeding warning in § 201.63 of this chapter.

(h) The ''Keep out of reach of children'' warning in § 330.1(g).

12. The agency is proposing the following directions for ibuprofen in § 343.10(g):

''• do not take more than directed [in bold type]
- adults and children 12 years and over:
- 200 milligrams[3] every 4 to 6 hours while symptoms persist
- if pain or fever does not respond to 200 milligrams[3], 400 milligrams[3] may be used
- do not exceed 1,200 milligrams[3] in 24 hours, unless directed by a doctor
- the smallest effective dose should be used
- children under 12 years: ask a doctor''.

[3]Convert number of milligrams to proper dosage.

VI. Labeling Guidance

In the **Federal Register** of March 17, 1999 (64 FR 13254), the agency published a final rule for standardized format and content requirements for OTC drug product labeling under § 201.66. An example of some aspects of the required format for labeling of OTC IAAA drug products containing ibuprofen appears in table 3 of this document. The ibuprofen labeling in the proposed amendment to the TFM (see the codified section of this document) appears in the new format.

VII. Implementation

Ibuprofen may be marketed only under an approved drug application prior to completion of a final rule for OTC IAAA drug products.

The agency encourages manufacturers to comply voluntarily with the provisions of this proposed rule for the labeling of OTC NSAID IAAA drug products that do not contain ibuprofen and that are marketed under an OTC drug TFM prior to the completion of a final rule, despite the fact that revisions in the requirements may occur in the final rule in response to submitted comments. Such labeling may be disseminated pending issuance of a final rule, subject to the risk that the agency may, in the final rule, adopt a different position that could require relabeling, recall, or other regulatory action. Should any manufacturer choose to adopt the labeling described in this proposed rule, and should any revisions occur in the final rule, the agency will permit the use of existing stocks of

labels for those products labeled according to this proposed rule for a period of 18 months following the publication of the final rule. Those manufacturers who do not wish to revise the labeling in accordance with this proposal may continue to use the labeling proposed in the 1988 TFM (53 FR 46204 at 46258 through 46260) until a final rule becomes effective.

VIII. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). 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. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the principles set out in the Executive order and in these two statutes. OMB has determined that the proposed rule is a significant regulatory action as defined by the Executive order. This economic analysis, together with other relevant sections of this document, serves as the agency's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation adjusted statutory threshold is about $110 million.

The purpose of this proposed rule is to include ibuprofen in the monograph for OTC IAAA drug products and to require consistent ''Allergy alert'' and additional allergy warning statements in the labeling of all OTC NSAID IAAA products. As most OTC NSAID IAAA products will be marketed under the final OTC IAAA monograph, these products will not have to include the allergy warnings in this proposal in product labeling until the final monograph is issued and becomes effective.

Current manufacturers of OTC 200-mg ibuprofen drug products should incur only minor one-time costs to relabel their products to meet the monograph. These costs may be offset by the elimination of the cost to maintain a market application, such as filing annual reports and submitting manufacturing supplements. Other manufacturers who may wish to market OTC 200-mg ibuprofen drug products would be able to enter the marketplace without the costs associated with obtaining an approved NDA/ANDA. Their costs would be those associated with the standard startup of any OTC drug marketed under the monograph system.

This proposed rule amends part 201 (21 CFR part 201) and will require relabeling for many OTC drug products containing NSAID IAAA ingredients. Most manufacturers that market such products under an approved NDA/ANDA already include the proposed ''Allergy alert'' and allergy warning statements in the product's labeling. Some manufacturers of these products, however, would have to revise the ''Allergy alert'' and allergy warning statements to conform to the proposed labeling. In addition, manufacturers of monograph products containing NSAID IAAA ingredients will have to relabel and include the revised allergy warnings in accord with the compliance dates specified in the IAAA products final rule. However, these allergy warnings are only one part of the overall labeling changes that will occur at that time when IAAA products are required to implement the standardized format and content requirements in § 201.66. The agency does not believe the proposed revised warnings will have a measurable impact on product usage.

The agency's analysis of impacts in the final rule that established the labeling requirements in § 201.66 applied only to products covered by the final OTC drug monographs or approved product applications (64 FR 13254 at 13283). Because these relabeling costs for OTC IAAA products have not been accounted for in earlier rules, the agency is presenting them here. The following discussion addresses the cost of product relabeling under § 201.66 that will result from the IAAA final monograph, which includes, in part, the labeling in this proposal.

Based on information in the agency's Drug Listing System, there are approximately 102 manufacturers and 322 distributors that together account for 2,000 to 2,400 OTC NSAID IAAA products. Assuming an average of 3 individual stockkeeping units (SKUs) (individual products, packages, and sizes) per product, up to 7,200 SKUs would require the allergy warnings. Estimates of relabeling costs for the type of changes required by the IAAA final monograph vary greatly and range from $500 to $15,000 per SKU depending on whether the products are nationally branded or private label. Because of the large number of products affected, the agency used the same weighted average cost to relabel (i.e., $3,600 per SKU)[1] that was used to estimate the cost of the standardized format and content requirements for OTC drug products in § 201.66 (64 FR 13254 at 13279 to 13281). Therefore, the estimated one-time cost to relabel these products is $25.9 million ($3,600 x 7,200 SKUs).

In addition to the above costs, some manufacturers may incur one-time and annually recurring costs if they need to increase the size of the label and/or package size of some SKUs because of the additional information required by this proposed rule. The agency had estimated that about 6,400 of the almost 100,000 marketed OTC drug SKUs may require increased label and/or package sizes to comply with the final labeling rule (64 FR 13254). As many of these 6,400 SKUs were for products subject to this final rule, much of the costs for increasing label and/or package sizes may have already been accounted for in the agency's impact analysis of that broader rule. The agency estimates that the additional lines of labeling required by this proposed rule could compel an additional 5 percent of the approximately 7,200 affected SKUs to increase their label size and/or package size.[2]

[1] The average weighted cost to relabel was calculated by using midpoint estimates of the cost to redesign labels and value of inventory losses of old labels by type of product and firm. The midpoint estimate for labeling design for large nationally branded SKUs is $10,000 per SKU, the midpoint estimate for smaller branded SKUs is $4,500 per SKU, and the cost to relabel private label SKUs is $1,261. About 10 percent of the SKUs are nationally branded goods, 20 percent are smaller branded products, and 70 percent of the SKUs are private label goods. The average label inventory loss is about $2,968 per SKU for nationally branded products and about $576 per SKU for smaller branded products and private label goods. (($10,000 x 0.10) + ($4,500 x 0.20) + ($1,261 x 0.70) + ($2,968 x 0.10) + ($576 x 0.90) = $3,598)

[2] FDA has assumed tht all 7,200 SKUs will need to be relabeled to accommodate the standardized

Continued

Because of the large number of products affected by this rule, the agency assumes that the average cost per SKU to increase label and/or package sizes would be similar to that previously estimated by FDA for its analysis of the standardized format and content requirements for OTC drug products in § 201.66 (64 FR 13254). The model used to estimate the cost to change label/package sizes for that rule was developed by Eastern Research Group, Inc. (ERG), a private economics consulting firm under contract to FDA (Ref. 160). ERG assigned probabilities to several options for package changes, including adding a carton (if not already present), adding a fifth panel, increasing the size of the packaging or switching to a nonstandard form of labeling such as peel-back or accordion labels. Where applicable, the cost for changing a container size included container inventory loss, adjustment of the packaging line, and stability testing. Based on this model, FDA had estimated that the cost to increase label/package sizes to comply with the standardized format and content requirements for OTC drug products in § 201.66 was $38.1 million for 6,313 SKUs, with an annual recurring cost of $11.5 million. Consequently the average per SKU one-time cost was $6,038, and the average per SKU recurring cost was $1,820. Under the same assumptions, this proposed rule would impose additional one-time costs for increasing label/package sizes of $2.2 million (0.05 x 7,200 SKUs x $6,038), with annual recurring costs of $0.7 million (0.05 x 7,200 SKUs x $1,820). Thus, FDA estimates the overall costs of the OTC IAAA final monograph, which would include the labeling in this proposed rule, and the labeling required under § 201.66 to be $28.1 million in one-time costs and $0.7 million in annual recurring costs.

The proposed rule would not require any new reporting and recordkeeping activities, and no additional professional skills are needed. The March 17, 1999, standardized format and content requirements final rule for OTC drug product labeling in § 201.66 (64 FR 13254) will have an effect on the labeling of most of these products. There are no Federal rules that duplicate, overlap, or conflict with the proposed rule.

This proposed rule should not have a significant economic impact on a substantial number of small entities. However, the agency lacks sales information for the affected companies to quantify the impact. The Small Business Administration has determined that a small firm in this industry employs fewer than 750 employees. Approximately 70 percent of the 102 manufacturers affected by this proposed rule are estimated to be small. (Note: The cost to relabel private label goods are usually bourne by the manufacturer rather than the distributor.) The economic impact on any particular small firm is difficult to measure, because it will vary with the number of products affected, the number of SKUs per product, and the number of label and/or package sizes that require changing. For example, if a small manufacturer must relabel three products, or nine SKUs, the total one-time cost would be $32,400 assuming $3,600 as the average cost to relabel. Another small manufacturer of private label products may also need to relabel 3 products, with 3 SKUs per product, but for 20 customers. Its cost would be $648,000. If either of these manufacturers had to increase the label and/or package sizes of their SKUs, the costs would be even higher. However, the total cost will primarily result from relabeling OTC IAAA drug products in accord with the future final monograph for those products and the standardized format and content requirements for labeling OTC drug products in § 201.66 (64 FR 13254) at the same time. The agency invites small firms to address this economic impact. (See section XI of this document—request for comments.)

Concerning the allergy alert warning, the agency considered but rejected the following alternatives: (1) Voluntary relabeling, and (2) longer implementation period. The agency does not consider either of these approaches acceptable because they do not ensure that consumers will have the most updated information needed for the safe and effective use of OTC drug products containing NSAID IAAA active ingredients. Concerning ibuprofen, the agency considered: (1) Not including ibuprofen in the monograph, and (2) marketing before a final rule is issued. The option to not include ibuprofen in the monograph was rejected because the agency considers the data presented supportive of monograph status. The agency is not allowing marketing under the monograph to occur prior to a final rule because of a number of new labeling statements being proposed. Not allowing marketing under this proposed rule does not interrupt current OTC marketing of products containing ibuprofen and will allow the agency to consider comments on the additional labeling for OTC ibuprofen drug products before finalizing the monograph labeling. The agency does not consider an exemption for small entities who wish to market ibuprofen to be necessary because those manufacturers or distributors can enter the marketplace under the monograph at any time after a final rule issues.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC drug products that contain ibuprofen or other NSAID IAAA active ingredients. Comments regarding the impact of this rulemaking on these OTC drug products should be accompanied by appropriate documentation. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements in this proposal are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling 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)).

X. Environmental Impact

The agency has 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.

XI. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding this proposal by November 19, 2002. Submit written comments on the agency's economic impact determination by November 19, 2002. Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this

format and content requirements in § 201.66 and the proposed warning. When calculating the cost of the standardized format and content requirements, FDA included the cost to increase the size of the label or the package size to accommodate the standardized format. As a result of this proposal, the warning adds additional lines of text to the label. FDA estimates that 5 percent of the 7,200 SKUs may require larger labels or package sizes to accommodate the additional text.

document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XII. Proposed Effective Date

FDA is proposing that any final rule based on this proposal become effective 12 months after the date of its publication in the **Federal Register** or at a later date if stated in the final rule. The compliance date for products with annual sales less than $25,000 would be 24 months after the date of publication of a final rule in the **Federal Register** or at a later date if stated in the final rule.

XIII. References

The following references are on display in the Dockets Management Branch (address above), under Docket No. 77N–094I (or 77N–0094, where indicated), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP13, Docket No. 77N–0094, Dockets Management Branch.

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6. Summary Basis of Approval for New Drug Application for Ibuprofen (200 mg), OTC Vol. 03BTFM(I), Docket No. 77N–094I, Dockets Management Branch.

7. Comment No. CP3, Docket No. 77N–0094, Dockets Management Branch.

8. Comment No. PDN002, Docket No. 77N–0094, Dockets Management Branch.

9. Memoranda of Telecon Between Representatives of Whitehall Robins Health Care and FDA on August 6, 1998, and August 26, 1998, coded MT12 and MT13, respectively, Docket No. 77N–0094, Dockets Management Branch.

10. Comment No. SUP44, Docket No. 77N–0094, Dockets Management Branch.

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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 343

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 201 and 343 be amended as follows:

PART 201—LABELING

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

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

2. Section 201.63 is amended by revising paragraph (e) to read as follows:

§ 201.63 Pregnancy/breast-feeding warning.

* * * * *

(e) The labeling of orally or rectally administered OTC aspirin- and ibuprofen-containing products must bear a warning that immediately follows the general warning identified in paragraph (a) of this section. The warning shall be as follows:

''It is especially important not to use'' [select ''aspirin,'' ''carbaspirin calcium,'' or ''ibuprofen,'' as appropriate] ''during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.''

3. Section 201.324 is added to subpart G to read as follows:

§ 201.324 Over-the-counter drug products containing internal analgesic/antipyretic active ingredients; required allergy warning statements.

The labeling for all over-the-counter (OTC) drug products containing nonsteroidal anti-inflammatory internal analgesic/antipyretic active ingredients—including but not limited to aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate—whether subject to an applicable OTC drug monograph or an approved drug application, contains the following allergy warnings under the heading ''Warnings'':

(a) ''Allergy alert: [insert name of active ingredient (first letter of first word for ingredient in uppercase)] may cause a severe allergic reaction which may include: [bullet][1] hives [bullet] facial swelling [bullet] asthma (wheezing) [bullet] shock''.

(b) ''Do not use [insert bullet if more than one warning occurs under this subheading] if you have ever had'' or for products labeled only for use in children under 12 years of age, ''Do not use [insert bullet if more than one warning occurs under this subheading] if your child has ever had'' followed by, ''an allergic reaction to any other pain reliever/fever reducer''. [This statement appears as the first warning under the subheading ''Do not use.'']

(c) ''Stop use and ask a doctor if [insert bullet if more than one warning occurs under this heading] an allergic reaction occurs. Seek medical help right away.'' [These statements appear as the first warning under the subheading ''Stop use and ask a doctor if.'']

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

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

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

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

5. Section 343.3 is amended by alphabetically adding a definition for ibuprofen to read as follows:

§ 343.3 Definitions.

* * * * *

Ibuprofen. A racemic mixture of the S-[+] and R-[-] enantiomers of ibuprofen in a tablet formulation for adults and children 12 years and older.

* * * * *

6. Section 343.10, as proposed at 53 FR 46255, November 16, 1988, is further amended by adding paragraph (g) to read as follows:

§ 343.10 Analgesic-antipyretic active ingredients.

* * * * *

(g) Ibuprofen 200-milligram tablet.

* * * * *

7. Section 343.20, as proposed at 53 FR 46255, November 16, 1988, is further is amended by revising paragraphs (b)(2) and (b)(4) to read as follows:

§ 343.20 Permitted combinations of active ingredients.

* * * * *

(b) * * *

(2) *Analgesic-antipyretic active ingredients identified in § 343.10(a) through (f) and cough-cold combinations.* See § 341.40 of this chapter.

* * * * *

(4) *Analgesic and diuretic combinations.* Any analgesic identified in § 343.10(a) through (f) or any combination of analgesics identified in § 343.20(a) may be combined with any diuretic identified in § 357.1012 of this chapter provided the product bears labeling indications in accordance with § 357.1060(b) of this chapter.

8. Section 343.50, as proposed at 53 FR 46255, November 16, 1988, is further is amended by revising the headings in paragraphs (b)(1), (c)(1)(i), and (c)(2)(i); and the text of paragraphs (c)(1)(iv)(A), (c)(1)(iv)(B), (c)(1)(vi), (c)(2)(iv)(A), and (c)(2)(vi); and by adding paragraphs (b)(5), (c)(1)(ix), and (d)(7) to read as follows:

§ 343.50 Labeling of analgesic-antipyretic drug products.

* * * * *

(b) * * *

(1) *For products containing any ingredient identified in § 343.10(a) through (f).* * * *

* * * * *

(5)*For products containing ibuprofen identified in § 343.10(g).* The labeling of the product contains any of the indications in § 343.50(b) except ''sore throat.''

(c) * * *

(1) * * *

(i) *For products containing any ingredient identified in § 343.10(a) through (f).* * * *

* * * * *

(iv) * * *

(A) ''Do not use this product if you have asthma unless directed by a doctor''.

(B) The labeling contains the pregnancy/breast-feeding warnings set forth in § 201.63(a) and (e) of this chapter.

* * * * *

(vi) *For products containing any ingredient identified in § 343.10(b) through (g).* The labeling of the product contains the allergy warnings set forth in § 201.324(a), (b), and (c) of this chapter.

* * * * *

(ix) *For products containing ibuprofen identified in § 343.10(g).* (A) The alcohol warning set forth in § 201.322(a)(2) of this chapter appears after the subheading ''Alcohol warning:.''

(B) ''Ask a doctor before use if you have: [bullet][1] problems or serious side effects from taking pain relievers or fever reducers [bullet] stomach problems that last or come back, such as heartburn, upset stomach, or pain [bullet] ulcers [bullet] bleeding problems [bullet] high blood pressure, heart or kidney disease, are taking a diuretic, or are over 65 years of age''.

(C) ''Ask a doctor or pharmacist before use if you are: [bullet] under a doctor's care for any serious condition [bullet] taking any other product that contains ibuprofen, or any other pain reliever/fever reducer [bullet] taking a prescription drug for anticoagulation (blood thinning) [bullet] taking any other drug''.

(D) ''When using this product: [insert bullet if more than one warning occurs under this subheading] take with food or milk if stomach upset occurs''.

(E) In addition to the warning required in § 201.324(c) of this chapter, the following statements appear after the subheading ''Stop use and ask a doctor if: [bullet] pain gets worse or lasts more than 10 days [bullet] fever gets worse or lasts more than 3 days [bullet] stomach pain gets worse or lasts [bullet] redness or swelling is present in the painful area [bullet] any new symptoms appear''.

(F) The labeling contains the pregnancy/breast-feeding warnings set forth in § 201.63(a) and (e) of this chapter.

(2) * * *

(i) *For products containing any ingredient identified in § 343.10(a) through (f).* * * *

* * * * *

(iv) * * *

(A) ''Do not give this product to children who have asthma unless directed by a doctor''.

* * * * *

(vi) *For products containing any ingredient in § 343.10(b) through (g).* The labeling contains the allergy warnings set forth in § 201.324(a), (b), and (c) of this chapter.

* * * * *

(d) * * *

* * * * *

(7) *For products containing ibuprofen identified in § 343.10(g).* The labeling states ''[bullet][1] do not take more than directed [in bold type] [bullet] adults and children 12 years and over: [bullet] 200 milligrams [2] every 4 to 6 hours while symptoms persist [bullet] if pain or fever does not respond to 200 milligrams[2], 400 milligrams[2] may be used [bullet] do not exceed 1,200 milligrams[2] in 24 hours, unless directed by a doctor [bullet] the smallest effective dose should be used [bullet] children under 12 years: ask a doctor''.

* * * * *

Dated: January 10, 2002.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02–21122 Filed 8–20–02; 8:45 am]

BILLING CODE 4160–01–S

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

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

[2] Convert number of milligrams to proper dosage.

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[AL–200234; FRL–7264–4]

Proposed Determination of Attainment of 1-hour Ozone Standard as of November 15, 1993, for the Birmingham, AL, Marginal Ozone Nonattainment Area

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA proposes to determine that the Birmingham marginal ozone nonattainment area (hereinafter referred to as the Birmingham area) attained the 1-hour ozone National Ambient Air Quality Standard (NAAQS) by November 15, 1993, the date required by the Clean Air Act (CAA). The Birmingham area is comprised of Jefferson and Shelby Counties. On July, 10, 2002, the United States District Court for the District of Columbia concluded that EPA failed to exercise its non-discretionary duty to make a final attainment determination for the Birmingham area by May 15, 1994. The Court required that EPA make a formal attainment determination within 120 days from date of opinion. *Sierra Club* v. *Whitman,* No. 00–2206 (D.D.C. July 10, 2002). Therefore, in response to the Court's order, EPA proposes to determine that the Birmingham area attained the 1-hour ozone standard by its statutory attainment date of November 15, 1993.

DATES: Written comments must be received on or before September 20, 2002.

ADDRESSES: All comments should be addressed to: Sean Lakeman; Regulatory Development Section; Air Planning Branch; Air, Pesticides and Toxics Management Division; U.S. Environmental Protection Agency Region 4; 61 Forsyth Street, SW, Atlanta, Georgia 30303–8960.

Copies of documents relative to this action are available at the following address for inspection during normal business hours: Environmental Protection Agency, Region 4, Air Planning Branch, 61 Forsyth Street, SW, Atlanta, Georgia 30303–8960.

The interested persons wanting to examine these documents should make an appointment at least 24 hours before the visiting day and reference file AL–200234.

FOR FURTHER INFORMATION CONTACT: Sean Lakeman, Regulatory Development Section, Air Planning Branch, Air, Pesticides and Toxics Management Division, Region 4, U.S. Environmental Protection Agency, 61 Forsyth Street, SW, Atlanta, Georgia 30303–8960. The telephone number is (404) 562–9043. Mr Lakeman can also be reached via electronic mail at *lakeman.sean@epa.gov.*

SUPPLEMENTARY INFORMATION:

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