



United States
CONSUMER PRODUCT SAFETY COMMISSION
 Washington, D.C. 20207

907 1007-5 P1 1997
 99711

VOTE SHEET

DATE: MAY 5 1997

TO : The Commission
 Sadye E. Dunn, Secretary

FROM : Jeffrey Bromme, General Counsel *J. Bromme*
 Stephen Lemberg, Assistant General Counsel *S. Lemberg*
 Patricia M. Pollitzer, Attorney, OGC *P. M. Pollitzer*

SUBJECT: Final PPPA Rule Requiring Child-Resistant Packaging
 for Ketoprofen

Attached is a staff briefing package recommending that the Commission issue a final rule requiring child-resistant packaging under the Poison Prevention Packaging Act ("PPPA") for the drug ketoprofen. Tab F of the package contains a draft Federal Register notice.

Please indicate your vote on the following options.

I. Approve the Federal Register notice as drafted.

 (Signature)

 (Date)

II. Approve the draft Federal Register notice with the following changes (please specify).

 (Signature)

 (Date)

NOTE: This document has not been reviewed or accepted by the Commission.
 Initial *rd* Date 5/5/97

CPSA 6 (b)(1) Cleared
5/5/97
 No Mfrs/Prvt. Lblrs. or
 Products Identified
 X Excepted *Bulenberg*

III. Do not approve the draft Federal Register notice.

(Signature)

(Date)

IV. Take other action (please specify).

(Signature)

(Date)

Attachment

Briefing Package

Final Rule to Require Child-Resistant
Packaging for Ketoprofen

For Information Contact:
Jacqueline Ferrante, Ph.D.
Directorate for Epidemiology and Health Sciences
(301) 504-0477

NOTE: This document has not been
reviewed or accepted by the Commission.

Initial rlh Date 5/5/97

CPSA 6 (b)(7) Cleared
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Executive Summary

In 1995, the Food and Drug Administration granted over-the-counter (OTC) status to ketoprofen, a nonsteroidal anti-inflammatory drug (NSAID). OTC drugs are not subject to the special packaging requirements of the Poison Prevention Packaging Act (PPPA). The Commission proposed a special packaging standard for products containing more than 50 mg of ketoprofen on November 20, 1996. The only comment the staff received supported the proposal.

Available data show that ketoprofen may cause serious injury or illness in humans. The two companies currently marketing OTC ketoprofen voluntarily use child-resistant packaging (CRP), demonstrating that the standard is technically feasible, practicable, and appropriate. A mandatory special packaging standard for ketoprofen would ensure that all current and future manufacturers use CRP that meets the performance standards of the PPPA test protocol. Moreover, the use of CRP will not be an economic burden for future small business marketers. For these reasons, the staff recommends that the Commission issue a final rule to require special packaging for all OTC preparations containing more than 50 mg of ketoprofen per package.



United States
CONSUMER PRODUCT SAFETY COMMISSION
 Washington, D.C. 20207

MAY 5 1997

To: The Commission
 Sadye E. Dunn, Secretary

Through: Jeffrey S. Bromme, General Counsel *[Signature]*
Through: Pamela Gilbert, Executive Director *PG*

From: *for* Ronald L. Medford, Assistant Executive Director for Hazard Identification and Reduction
 Jacqueline N. Ferrante, Ph.D., Pharmacologist, Directorate for Epidemiology and Health Sciences, Division of Poison Prevention and Scientific Coordination

Subject: Special Packaging Standard for Ketoprofen

I. Introduction

The Food and Drug Administration (FDA) granted over-the-counter (OTC) status to ketoprofen, a nonsteroidal anti-inflammatory drug (NSAID), on October 6, 1995. Although child-resistant packaging (CRP) was required for ketoprofen as an oral prescription drug, the formulation available for OTC use is not subject to the special packaging requirements of the Poison Prevention Packaging Act (PPPA). On November 20, 1996, the Commission issued a proposed rule that would require CRP for OTC drugs containing more than 50 milligrams (mg) of ketoprofen (Tab A).

II. Background

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) used for the temporary relief of minor aches and pains associated with the common cold, headaches, toothaches, muscular aches, arthritis, and menstrual cramps. The OTC formulations, ketoprofen and ketoprofen tartrazine, contain 12.5 milligrams (mg) of ketoprofen per tablet. These formulations are not recommended for children under 16 years old unless directed by a physician.

The Commission previously established special packaging standards for ibuprofen and naproxen, two other NSAIDs granted OTC status. Typical adverse effects associated with NSAIDs include nausea, vomiting, constipation, abdominal pain, diarrhea, headache, and dizziness. Additionally, NSAIDs may cause serious adverse effects such as gastrointestinal (GI) bleeding or perforation, GI ulceration, and renal injury. Detailed toxicity and poisoning

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 Products Identified
 Exempted by *[Signature]*

information relating to ketoprofen was provided to the Commission in a briefing package dated October 15, 1996.

The patent for ketoprofen expired in 1993. Two companies are voluntarily marketing OTC formulations of ketoprofen in CRP. A mandatory special packaging standard for ketoprofen would ensure that future marketers use CRP that meets the performance requirements of the PPPA.

III. Discussion

A. Public Comments

The Commission received one comment in response to the proposed rule (Tab B). The American Society of Health-System Pharmacists (ASHP) expressed support for the proposal. The ASHP agreed that ketoprofen may cause serious harm to children and that the proposed rule is consistent with special packaging requirements for other OTC NSAIDs.

B. Updated Injury Data

The staff updated poisoning information from the National Electronic Injury Surveillance System (NEISS) and the American Association of Poison Control Centers (AAPCC) (Tab B). The NEISS database consists of all consumer product-related cases treated in a sample of hospital emergency rooms and the AAPCC documents all telephone calls to poison control centers.

From 1988 to June 1996, three cases involving ketoprofen in children under five years old were found in the NEISS database. None of the cases were fatal or required hospitalization and all three occurred in 1996. Since that time, seven new cases of children who ingested ketoprofen were documented through NEISS. All seven children were treated and released. Three cases involved the OTC formulation of ketoprofen.

From 1985 to 1994, American Association of Poison Control Center (AAPCC) data involving ketoprofen were not categorized separately from other NSAIDs, unless they resulted in death. During that time period no deaths were reported from ketoprofen. In 1995, the staff requested a separate report from the AAPCC which showed 250 accidental ingestions of

ketoprofen involving children under five years old. Twelve of these resulted in minor outcomes¹. There were no moderate outcomes², major outcomes³, or deaths resulting from these ketoprofen incidents.

C. Level for Regulation

The level for regulation is based on guidelines established for pediatric NSAID overdose, which recommend medical treatment for young children who ingest five times the maximum single therapeutic dose. The maximum single therapeutic dose for ketoprofen is 75 mg or 1.08 mg/kg assuming an average adult weight of 70 kg. Therefore, the dose of ketoprofen requiring medical intervention would be five times the maximum single therapeutic dose (1.08 mg/kg), which in a 10-kg child would be more than 50 mg of ketoprofen (four OTC tablets).

D. Regulatory Flexibility Issues

The Directorate for Economic Analysis concluded that a requirement for special packaging of OTC ketoprofen products will not have a significant economic effect on a substantial number of small businesses (Tab C). The two companies currently marketing these products are voluntarily using CRP. Cost should not be an entry barrier for future small business marketers of ketoprofen since senior-friendly CRP is readily available at a low incremental cost.

E. Technical Feasibility, Practicability, and Appropriateness

The Directorate for Epidemiology and Health Sciences concludes that special packaging for OTC ketoprofen products is technically feasible (producible), practicable (lends itself to mass production techniques), and appropriate (compatible with the product) (Tab D). The two manufacturers of OTC ketoprofen are voluntarily using continuous threaded and snap-type packaging that have been shown to be senior-friendly. Additionally, one company uses pouch packaging for a sample size that is child-resistant and has a senior-friendly scissors opening option.

¹ The patient exhibited minimal signs or symptoms which resolved rapidly.

² The patient exhibited symptoms that were more pronounced, prolonged, or of a systemic nature which usually required treatment.

³ The patient exhibited symptoms which were life-threatening or resulted in residual disability.

F. Effective Date

The PPPA provides that no regulation shall take effect sooner than 180 days or later than one year from the date such regulation is issued, unless the Commission determines that an earlier effective date is in the public interest. For ketoprofen, an effective date of 180 days after the issuance of a final rule is reasonable since adequate supplies of the new senior-friendly CRP are available.

IV. Options

The Commission may issue a rule requiring special packaging for OTC products containing more than 50 mg of ketoprofen in a single container if the Commission finds that:

- 1) special packaging is required to protect young children from serious personal injury or illness from handling, using, or ingesting the product; and
- 2) special packaging is technically feasible, practicable, and appropriate.

The Commission may decline to issue a special packaging rule for ketoprofen if it is unable to make these findings.

V. Recommendation

Ketoprofen is a NSAID that may cause serious toxicity if accidentally ingested by small children. The greater availability of ketoprofen as an OTC drug may increase the likelihood of accidental ingestions in young children. The current marketers of OTC ketoprofen are voluntarily using CRP. However, a mandatory requirement would ensure that future manufacturers of OTC ketoprofen use CRP and that this packaging meets the performance standards established by the Commission. The staff recommends that the Commission issue a special packaging standard for all OTC products with more than 50 mg of ketoprofen per package.

A draft final rule prepared by the Office of the General Counsel is at Tab F.

A

Counsel, Western Pacific Region, Federal Aviation Administration, Room 6007, 15000 Aviation Boulevard, Lawndale, California 90261.

An informal docket may also be examined during normal business at the Office of the Manager, Operations Branch, Air Traffic Division at the above address.

FOR FURTHER INFORMATION CONTACT: William Buck, Airspace Specialist, Operations branch, AWP-530, Air Traffic Division, Western-Pacific Region, Federal Aviation Administration, 15000 Aviation Boulevard, Lawndale, California 90261, telephone (310) 725-6556.

SUPPLEMENTARY INFORMATION:
Comments Invited

Interested parties are invited to participate in this proposed rulemaking by submitting such written data, views, or arguments as they may desire. Comments that provide the factual basis supporting the views and suggestions presented are particularly helpful in developing reasoned regulatory decisions on the proposal. Comments are specifically invited on the overall regulatory, aeronautical, economic, environmental, and energy-related aspects of the proposal. Communications should identify the airspace docket number and be submitted in triplicate to the address listed above. Commenters wishing the FAA to acknowledge receipt of their comments on this notice must submit with the comments a self-addressed, stamped postcard on which the following statement is made: "Comments to Airspace Docket No. 96-AWP-30." The postcard will be date/time stamped and returned to the commenter. All communications received on or before the specified closing date for comments will be considered before taking action on the proposed rule. The proposal contained in this notice may be changed in light of comments received. All comments submitted will be available for examination in the Operations Branch, Air Traffic Division, at 15000 Aviation Boulevard, Lawndale, California 90261, both before and after the closing date for comments. A report summarizing each substantive public contact with FAA personnel concerned with this rulemaking will be filed in the docket.

Availability of NPRM

Any person may obtain a copy of this Notice of Proposed Rulemaking (NPRM) by submitting a request to the Federal Aviation Administration, Operations Branch, P.O. Box 92007, Worldway

Postal Center, Los Angeles, California 90009. Communications must identify the notice number of this NPRM. Persons interested in being placed on a mailing list for future NPRM's should also request a copy of Advisory Circular No. 11-2A, which describes the application procedures.

The Proposal

The FAA is considering an amendment to part 71 of the Federal Aviation Regulations (14 CFR part 71) to revise the Class E airspace area at Victorville, CA. The closure of George Air Force Base has made this proposal necessary. The intended effect of this proposal is to redefine the controlled airspace necessary for IFR operations at Southern California International Airport, Victorville, CA. Class E airspace designations are published in Paragraph 6005 of FAA Order 7400.9D dated September 4, 1996 and effective September 16, 1996, which is incorporated by reference in 14 CFR 71.1. The Class E airspace designation listed in this document would be published subsequently in this Order.

The FAA has determined that this proposed regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. Therefore, this proposed regulation—(1) is not a "significant regulatory action" under Executive Order 12866; (2) is not a "significant rule" under DOT Regulatory Policies and Procedures (44 FR 10034; February 26, 1979); and (3) does not warrant preparation of a Regulatory Evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified that this proposed rule would not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—[AMENDED]

1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959-1963 Comp., p. 389; 14 CFR 11.69.

§71.1 [Amended]

2. The incorporation by reference in 14 CFR 71.1 of the Federal Aviation Administration Order 7400.9D, Airspace Designations and Reporting Points, dated September 4, 1996, and effective September 16, 1996, is amended as follows:

Paragraph 6005 Class E Airspace

* * * * *

AWP CA E Victorville, CA [Revised]
Victorville, Southern California International Airport, CA
(Lat. 34°35.67'N, long. 117°22.93'W)

That airspace extending upward from 700 feet above the surface within a 6-mile radius of the Victorville, Southern California International Airport, CA.

* * * * *

Issued in Los Angeles, California, on November 4, 1996.

Sabra W. Kaulia,

Assistant Manager, Air Traffic Division, Western-Pacific Region.

[FR Doc. 96-29683 Filed 11-19-96; 8:45 am]

BILLING CODE 4910-13-M

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

Proposed Rule: Requirements for Child-Resistant Packaging; Packages Containing More Than 50 mg of Ketoprofen

AGENCY: Consumer Product Safety Commission.

ACTION: Proposed rule.

SUMMARY: The Commission is proposing a rule to require child-resistant packaging for ketoprofen preparations containing more than 50 mg of ketoprofen per retail package. Ketoprofen is a nonsteroidal anti-inflammatory drug and is used to relieve minor aches and pains and to reduce fever. The Commission has preliminarily determined that child-resistant packaging is necessary to protect children under 5 years of age from serious personal injury and serious illness resulting from ingesting ketoprofen. The Commission takes this action under the authority of the Poison Prevention Packaging Act of 1970.

DATES: Comments on the proposal should be submitted no later than February 3, 1997.

ADDRESSES: Comments should be mailed to the Office of the Secretary, Consumer Product Safety Commission, Washington, DC 20207, or delivered to the Office of the Secretary, Consumer Product Safety Commission, Room 502.

4330 East-West Highway, Bethesda, Maryland 20814-4408, telephone (301) 504-0800.

FOR FURTHER INFORMATION CONTACT: Jacqueline Ferrante, Ph.D., Division of Poison Control and Scientific Coordination, Directorate for Health Sciences, Consumer Product Safety Commission, Washington, DC 20207; telephone (301) 504-0477 ext. 1199.

SUPPLEMENTARY INFORMATION:

A. Background

1. Relevant Statutory and Regulatory Provisions

The Poison Prevention Packaging Act of 1970 ("PPPA"), 15 U.S.C. 1471-1476, authorizes the Commission to establish standards for the "special packaging" of any household substance if (1) the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance and (2) the special packaging is technically feasible, practicable, and appropriate for such substance.

Special packaging, also referred to as "child-resistant (CR) packaging," is packaging that (1) is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and (2) is not difficult for "normal adults" to use properly. 15 U.S.C. 1471(4). Household substances for which the Commission may require CR packaging include (among other categories) foods, drugs, or cosmetics as these terms are defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321). 15 U.S.C. 1471(2)(B). The Commission has performance requirements for special packaging. 16 CFR 1700.15, 1700.20.

Section 4(a) of the PPPA, 15 U.S.C. 1473(a), allows the manufacturer or packer to package a nonprescription product subject to special packaging standards in one size of non-CR packaging only if the manufacturer (or packer) also supplies the substance in CR packages of a popular size, and the non-CR packages bear conspicuous labeling stating: "This package for households without young children." 15 U.S.C. 1473(a), 16 CFR 1700.5.

2. Ketoprofen

Ketoprofen is a nonsteroidal anti-inflammatory drug ("NSAID"). This class of compounds also includes ibuprofen and naproxen. Ketoprofen is

used to relieve minor aches and pains such as those associated with colds, toothaches, menstrual cramps, and muscular aches. It is also used to reduce fever.[2]¹

For the past ten years, ketoprofen has been a prescription drug. Like all prescription drugs, it was required to be in child-resistant packaging by the Commission's regulation of human oral prescription drugs, 16 CFR 1700.14(a)(10). The U.S. patent on ketoprofen expired in 1993. On October 6, 1995, the Food and Drug Administration ("FDA") granted nonprescription ("over-the-counter," or "OTC") status to ketoprofen. [2]

The OTC formulations, ketoprofen and ketoprofen tartrazine, contain 12.5 milligrams (mg) of ketoprofen per dose. The recommended dose is 1 tablet every 4 to 6 hours. The maximum daily dose is 6 tablets. The drug is not recommended for children under 16 years old except under the supervision of a doctor. OTC ketoprofen should not be used (1) with any other analgesic or anti-pyretic, (2) for more than 3 days for fever, (3) for more than 10 days for pain, or (4) during the last trimester of pregnancy unless directed by a physician. [2]

3. Special Packaging

The current marketers are voluntarily placing ketoprofen in child-resistant packaging. However, a mandatory special packaging standard for ketoprofen products would ensure that other companies that may market such products in the future would use CR packaging.

Two other NSAIDs that previously became available OTC are ibuprofen and naproxen. After ibuprofen was introduced OTC, there was an increased incidence of accidental ingestions of the drug by children under 5. [2]

In part to avoid a similar experience with naproxen, in 1995, the Commission then issued a rule requiring CR packaging for naproxen preparations containing 250 mg or more per retail package. 60 FR 38671. The rule became effective February 6, 1996. Similar reasoning applies to ketoprofen.

A mandatory standard for ketoprofen would also enable the Commission to ensure that the packaging used meets the performance requirements of the PPPA test protocol at 16 CFR 1700.15, 1700.20.

B. Toxicity of Ketoprofen

The Commission's Directorate for Epidemiology and Health Sciences

reviewed the toxicity of ketoprofen. Side effects commonly associated with ketoprofen, as with other NSAID's, are gastrointestinal (GI) complications. These include nausea, vomiting, diarrhea, constipation, heartburn, and abdominal pain. Other common adverse effects include headache, dizziness, visual disturbances, rash, and hypersensitivity reactions.[2]

Ketoprofen may also cause more severe adverse GI effects, such as gastric or duodenal ulcer with bleeding or perforation; intestinal ulcers; ulcerative stomatitis or colitis; gingival ulcer; perforation and hemorrhage of the esophagus, stomach, small or large intestine; hematemesis; and rectal bleeding. Renal injuries also may result from chronic use of ketoprofen.[2]

The staff reviewed the relevant medical literature which cites several cases of severe adverse reactions to ketoprofen administration. In one case, a 61 year old woman suffered acute renal failure after taking 400 mg of ketoprofen daily for 10 days. She recovered after peritoneal dialysis. In addition, the literature reports one case of pancreatitis after 12 days of ketoprofen therapy and two cases of ketoprofen induced hepatitis. Other cases reported in the literature involved co-ingestion of other substances.[2]

The FDA maintains a data base known as the Adverse Events Reporting System ("AERS") for reports of adverse reactions detected after marketing a drug or biological product. Drug manufacturers are required to report to the FDA any known adverse effects associated with their products, but only an estimated 1% of all adverse reactions are actually reported. Also, reports may reflect effects from an underlying disease process or a reaction to multiple drugs. Of the 903 ketoprofen-associated cases reported to the FDA between 1986 and October 1995, the most common adverse reactions were abdominal pain (122), diarrhea (87), nausea (82), GI hemorrhage (70), rash (55), indigestion (39), labored breathing (34), allergic reaction (30), dizziness (30), and hives (30).[2]

Among the ketoprofen cases in the AERS database are 51 more serious reactions, i.e., hospitalizations, reactions resulting in permanent disability, or deaths. Five of these involved children under 16 years of age. Three 15 year old children required hospitalization for severe renal injury, and one 15 year old suffered a life-threatening GI hemorrhage and perforation. These events followed 10-18 days of therapy with daily doses of 200-225 mg ketoprofen. A 10 year old also required hospitalization for severe

¹ Numbers in brackets refer to documents listed at the end of this notice.

vision abnormalities after 15 days of treatment with 150 mg ketoprofen.[2]

The medical literature reports 2 overdoses, both involving other substances as well. In one case, a 12 year old girl ingested an unknown amount of ketoprofen plus 12 hydrocodone/acetaminophen tablets. She developed tonic-clonic seizures with loss of consciousness and metabolic acidosis. The symptoms resolved within 2 hours and she recovered fully. In the other incident, an adult ingested 12 capsules of sustained release ketoprofen 200 mg (total=2.4 grams) with 375 milliliters (12.5 ounces) of vodka. Only mild effects resulted since the victim vomited within 1 hour of the ingestion.[2]

The AERS database reports no pediatric ketoprofen overdoses, but there were some incidents involving adults. One intentional overdose of 1,000 mg ketoprofen resulted in moderate to severe kidney injury (kidney pain, bloody urine, increase creatinine levels). Ingestion of 500 mg of ketoprofen plus an unknown amount of ciprofloxacin produced death in a 50 year old woman. The symptoms which included GI hemorrhage, thrombocytopenia, coagulation disorders, and decreased prothrombin, were most likely related to ketoprofen.[2]

The AERS system also reports two neonatal poisoning cases in which the mothers took ketoprofen at some point in their pregnancy. One infant died shortly after birth from acute renal failure. In the second case (which involved multiple medications) twins developed acute renal failure shortly after birth. One twin died and the other recovered but was neurologically impaired.[2]

The staff reviewed accidental ingestion data for children under age 5. The American Association of Poison Control Center ("AAPCC") collects incident data through its Toxic Exposure Surveillance System ("TESS") which covers incidents from 1985 to 1994. Poisoning incidents involving ketoprofen are not recorded separately from other NSAIDs unless they were fatal. No deaths involving ketoprofen were reported during this period.[2]

CPSC's data base, the National Electronic Injury Surveillance System ("NEISS") monitors emergency room visits to selected hospitals throughout the United States. Review of NEISS data from 1988 to June 1996 shows three cases involving ketoprofen and children under 5 years old. All three incidents occurred in 1996; None were fatal or required hospitalization.[2]

C. Level for Regulation

The Commission is proposing a rule that requires special packaging for OTC ketoprofen products containing more than 50 mg ketoprofen per retail package. This level is based on established guidelines for medical treatment following pediatric ingestion of NSAID's.[5] These guidelines suggest medical treatment for young children who ingest five times the maximum single therapeutic dose. For ketoprofen, the maximum single therapeutic dose is 75 mg or 1.08 mg/kg assuming an average adult weight of 70 kg. The dose of ketoprofen requiring medical intervention would be five times 1.08 mg/kg, which in a 10-kg child would be more than 50 mg of ketoprofen, or four OTC tablets.[2]

D. Statutory Considerations

1. Hazard to Children

As noted above, the toxicity data concerning children's ingestion of ketoprofen demonstrate that this compound can cause serious illness and injury to children. Moreover, the preparations are readily available to children. The Commission preliminarily concludes that a regulation is needed to ensure that products subject to the regulation will be placed in CR packaging by any new manufacturers. In addition, the regulation will enable the Commission to enforce the CR packaging requirement and ensure that effective CR packaging is used.

Pursuant to section 3(a) of the PPPA, 15 U.S.C. 1472(a), the Commission preliminarily finds that the degree and nature of the hazard to children from ingesting ketoprofen is such that special packaging is required to protect children from serious illness. The Commission bases this finding on the toxic nature of these products, described above, and their accessibility to children in the home.

2. Technical Feasibility, Practicability, and Appropriateness

In issuing a standard for special packaging under the PPPA, the Commission is required to find that the special packaging is "technically feasible, practicable, and appropriate." 15 U.S.C. 1472(a)(2). Technical feasibility may be found when technology exists or can be readily developed and implemented by the effective date to produce packaging that conforms to the standards. Practicability means that special packaging complying with the standards can utilize modern mass production and assembly line techniques. Packaging is appropriate when complying packaging will

adequately protect the integrity of the substance and not interfere with its intended storage or use.[4]

The current marketers of OTC ketoprofen voluntarily use packaging that is child resistant. Similar designs have been shown to meet the revised testing protocol for senior adult use effectiveness. Therefore, the Commission concludes that CR packaging for ketoprofen is technically feasible, practicable, and appropriate.[3]

3. Other Considerations

In establishing a special packaging standard under the PPPA, the Commission must consider the following:

- The reasonableness of the standard;
- Available scientific, medical, and engineering data concerning special packaging and concerning childhood accidental ingestions, illness, and injury caused by household substances;
- The manufacturing practices of industries affected by the PPPA; and
- The nature and use of the household substance. 15 U.S.C. 1472(b).

The Commission has considered these factors with respect to the various determinations made in this notice, and preliminarily finds no reason to conclude that the rule is unreasonable or otherwise inappropriate.

E. Effective Date

The PPPA provides that no regulation shall take effect sooner than 180 days or later than one year from the date such final regulation is issued, except that, for good cause, the Commission may establish an earlier effective date if it determines an earlier date to be in the public interest. 15 U.S.C. 1471n.

The Commission does not believe that a shorter effective date is necessary to protect the public interest. The companies that are currently marketing ketoprofen are voluntarily using CR packaging. The Commission does not have any indication that significant quantities of ketoprofen will be marketed in non-CR packaging before a 180 day effective date, except for a single size non-CR package as allowed under the PPPA. Thus, the Commission finds that a 180 day effective date is consistent with the public interest and proposes that a final rule would take effect 180 days after publication of the final rule. A final rule would apply to products that are packaged on or after the effective date.

F. Regulatory Flexibility Act Certification

When an agency undertakes a rulemaking proceeding, the Regulatory Flexibility Act, 5 U.S.C. 601 et seq.,

generally requires the agency to prepare proposed and final regulatory flexibility analyses describing the impact of the rule on small businesses and other small entities. Section 605 of the Act provides that an agency is not required to prepare a regulatory flexibility analysis if the head of an agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

The Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of a rule to require special packaging for ketoprofen preparations with more than 50 mg ketoprofen in a single package. Based on this assessment, the Commission concludes that such a requirement would not have a significant impact on a substantial number of small businesses or other small entities because the current marketers of ketoprofen are using CR packaging. Furthermore, the relatively low costs of CR packages should not be an entry burden for future marketers.

G. Environmental Considerations

Pursuant to the National Environmental Policy Act, and in accordance with the Council on Environmental Quality regulations and CPSC procedures for environmental review, the Commission has assessed the possible environmental effects associated with the proposed PPPA requirements for ketoprofen preparations.

The Commission's regulations state that rules requiring special packaging for consumer products normally have little or no potential for affecting the human environment. 16 CFR 1021.5(c)(3). Therefore, because the rule would have no adverse effect on the environment, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

For the reasons given above, the Commission proposes to amend 16 CFR part 1700 as follows:

PART 1700—[AMENDED]

1. The authority citation for part 1700 continues to read as follows:

Authority: Pub. L. 91-601, secs. 1-9, 84 Stat. 1670-74, 15 U.S.C. 1471-76. Secs. 1700.1 and 1700.14 also issued under Pub. L. 92-573, sec. 30(a), 88 Stat. 1231, 15 U.S.C. 2079(a).

2. Section 1700.14 is amended by adding new paragraph (a)(25), reading

as follows (although unchanged, the introductory text of paragraph (a) is republished below for context):

§ 1700.14 Substances requiring special packaging.

(a) Substances. The Commission has determined that the degree or nature of the hazard to children in the availability of the following substances, by reason of their packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substances, and the special packaging herein required is technically feasible, practicable, and appropriate for these substances:

* * * * *

(25) Ketoprofen. Ketoprofen preparations for human use and containing more than 50 mg of ketoprofen in a single retail package shall be packaged in accordance with the provisions of § 1700.15 (a), (b), and (c).

* * * * *

Dated: November 15, 1996.

Sadye E. Dunn,

Secretary, Consumer Product Safety Commission.

List of Relevant Documents

1. Briefing memorandum from Jacqueline Ferrante, Ph.D., HSPS, to the Commission. "Proposed Rule to Require Child-Resistant Packaging for Ketoprofen," October 15, 1996.

2. Memorandum from Susan C. Aitken, Ph.D., HSHE, to Jacqueline Ferrante, Ph.D., HSPS. "Toxicity of Ketoprofen." August 19, 1996.

3. Memorandum from Marcia P. Robins, ECSS, to Jacqueline Ferrante, Ph.D., HSPS. "Preliminary Assessment of Economic and Environmental Effects of a Proposal to Require Child-Resistant Packaging for OTC Pharmaceuticals Containing Ketoprofen." August 19, 1996.

4. Memorandum from Charles Wilbur, HSPS, to Jacqueline Ferrante, Ph.D., HSPS. "Technical Feasibility, Practicability, and Appropriateness Determination for the Proposed Rule to Require Child-Resistant Packaging for OTC Products Containing Ketoprofen." August 20, 1996.

5. Vale, J.S. and Meredith, T.J. Acute Poisoning Due to Non-steroidal Anti-inflammatory Drugs: Clinical Features and Management. *Med. Toxicol.* 1:12-31, 1986.

[FR Doc. 96-29691 Filed 11-19-96; 8:45 am]

BILLING CODE 6355-01-P

SECURITIES AND EXCHANGE COMMISSION

17 CFR Parts 232 and 240

[Release No. 34-37949; File No. S7-21-96]

RIN 3235-AG99

Lost Securityholders

AGENCY: Securities and Exchange Commission.

ACTION: Extension of the comment period.

SUMMARY: The Securities and Exchange Commission ("Commission") is extending from October 28, 1996, until November 27, 1996, the comment period for Securities Exchange Act Release No. 37595 (August 22, 1996), 61 FR 44249 (August 28, 1996). In the release the Commission proposed two rules which are designed to address the problem of "lost securityholders."
DATES: Comments on the release should be submitted on or before November 27, 1996.

ADDRESSES: Comments should be submitted in triplicate to Jonathan G. Katz, Secretary, Securities and Exchange Commission, 450 Fifth Street, NW, Washington DC 20549, and should refer to File No. S7-21-96. Comments also may be submitted electronically at the following E-mail address: rule-comments@sec.gov. The file number should be included on the subject line if E-mail is used. Comment letters will be available for public inspection and copying at the Commission's public reference room, 450 Fifth St., NW, Washington DC 20549. Electronically submitted comment letters will be posted on the Commission's Internet Web site (<http://www.sec.gov>).

FOR FURTHER INFORMATION CONTACT: Jerry W. Carpenter, Assistant Director; Christine Sibille, Senior Counsel; or Michele Bianco, Attorney; at 202/942-4187, Office of Risk Management and Control, Mail Stop 5-1, Division of Market Regulation, Securities and Exchange Commission, Washington, DC 20549.

SUPPLEMENTARY INFORMATION: On August 22, 1996, the Commission proposed two rules designed to address the problem of securityholders for whom a transfer agent or broker-dealer no longer has a current address. Rule 17Ad-17 would require transfer agents to conduct searches in an effort to locate lost securityholders. Rule 17a-24 would allow the Commission to gather data related to lost securityholders and to provide it to information distributors or others. The Commission also is seeking



B





AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS

Pharmacists in health systems helping people make the best use of medications

CPSA 6/16/97
2/26/97
Products
Excepted
Firms Notified
Comments Processed

January 30, 1997

Office of the Secretary
Consumer Product Safety Commission
4330 East-West Highway, Room 502
Bethesda, MD 20814-4408

RE: 16 CFR 1700: Proposed Rule: Requirements for Child-Resistant Packaging;
Packages Containing More Than 50 mg of Ketoprofen

TO WHOM IT MAY CONCERN:

The American Society of Health-System Pharmacists (ASHP) is pleased to provide comments on the Consumer Product Safety Commission's proposed rule, issued on November 20, 1996, requiring child-resistant packaging for Ketoprofen preparations containing 50 mg or more of Ketoprofen per retail package. ASHP is the 30,000-member national professional association that represents pharmacists who practice in hospitals, health maintenance organizations, long-term care facilities, home care agencies, and other components of health care systems. This submission reflects comments received from ASHP members who reviewed the proposed rule.

ASHP supports the proposed rule. The toxicity data concerning children's ingestion of Ketoprofen demonstrate that this compound can cause serious illness and injury to children. The proposed rule is consistent with packaging rules for other over-the-counter nonsteroidal anti-inflammatory drugs.

ASHP's only concern relates to elderly patients who have severe arthritis and may struggle with child-proof packaging. They should be encouraged to work with their pharmacists to have the drug placed in more manageable packaging.

ASHP appreciates the opportunity to comment on this proposed rule. Feel free to contact me if you have any questions regarding our comments.

Sincerely,

Gary C. Stein, Ph.D.
Senior Government Affairs Associate

q:\regsl\other\ketoprof.com:sc

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UNITED STATES GOVERNMENT

MEMORANDUM

U.S. CONSUMER PRODUCT
SAFETY COMMISSION

WASHINGTON, D.C. 20207

MAR 4 1997

TO : Jacqueline Ferrante, Ph.D., Pharmacologist, Division of Poison Control
and Scientific Coordination

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for
Epidemiology and Health Sciences *mad*

THROUGH: Marilyn L. Wind, Ph.D., Director, Division of Poison Control and *mlw*
Scientific Coordination

FROM : Susan C. Aitken, Ph.D., Pharmacologist, Division of Poison Control and
Scientific Coordination *SCA*

SUBJECT: Update of Injuries Due to Accidental Ingestion of Ketoprofen Products

Staff reviewed the Consumer Product Safety Commission (CPSC) data bases between June 1, 1996 and February 22, 1997 to identify accidental ingestions of ketoprofen, naproxen or naproxen sodium, and ibuprofen by children less than 5 years old. An updated table summarizing data for all three non-steroidal anti-inflammatory agents (NSAIDs) is attached (Table 1). The updated Toxic Exposure Surveillance System (TESS) data from the American Association of Poison Control Centers (AAPCC) are also attached (Table 2).

Ketoprofen

Seven additional accidental ingestions of ketoprofen products by children less than 5 years old were identified in the National Electronic Injury Surveillance System (NEISS) data base during the past 8 months. All seven victims were treated and released. At least three of these ingestions involved the over-the-counter (OTC) formulation of 12.5 mg tablets. One child experienced sleepiness after the possible ingestion of as many as 20 OTC tablets. No incidents involving ketoprofen products were identified in the Injury and Potential Injury Incident (IPII) file, the death certificate file (DCRT), or the In-Depth Investigation (INDP) file. This brings the total number of ketoprofen ingestions to ten since the Food and Drug Administration (FDA) granted OTC status for the 12.5 mg formulation in 1994. No accidental ingestions of ketoprofen products were reported to the CPSC prior to this date.

Naproxen or Naproxen Sodium

The NEISS data base contains records of twelve additional ingestions of naproxen tablets between June, 1996 and February 22, 1997. Eleven children were treated and released. One child was hospitalized, but this child simultaneously ingested two extremely toxic drugs, Vasotec and Procardia. Two of these ingestions definitely involved the OTC formulation and an additional seven possibly may have involved the OTC formulation. No additional records were located in the IPII, DTSH, or INDP files.

Ibuprofen

Staff identified 59 additional ingestions of ibuprofen products by children less than 5 years old. Five cases involved prescription tablet formulations, eighteen involved OTC tablets, and twelve were not clearly identified as involving OTC or prescription tablets. Seventeen reports implicated liquid formulations; eight of these were identified as OTC products. The remaining seven ingestions involved unknown formulations of ibuprofen products. Two children required hospitalization. One of these children ingested additional medications (diet pills and tylenol); therefore, the proximate cause of the hospitalization was not clear. No additional cases of ibuprofen ingestion were identified in the IPII, DTSH, or INDP files.

The TESS data are shown in Table 2. Staff notes that the data isolating naproxen became available in 1993 and the data isolating ketoprofen were obtained only in 1995. Prior to these dates, both NSAIDs were included in the general category of "other non-steroidal anti-inflammatory drugs". The numbers for this "other NSAIDs" category reported by the AAPCC still include the ketoprofen and naproxen categories. However, staff specifically requested additional separate reports for naproxen and ketoprofen. The TESS data do not separate prescription and OTC formulations for ketoprofen products because the trade name, Orudis[®], is common to both an OTC and prescription product.

**Table 1. Injuries by Year in Children less than 5 Years Old.
(CPSC data bases, 1988- February 22, 1997)**

<u>Year</u>	<u>Ketoprofen</u>	<u>Naproxen</u>	<u>Ibuprofen</u>
1988	0	0	23
1989	0	1	29
1990	0	5	28*
1991	0	3	59
1992	0	0	26 xxxx 25
1993	0	2 ----	55
1994	0	3	68
1995	0	6 xxxx	92
1996	10	16	49
1997 (February 22)	0	1	10

* refers to a fatality due to aspiration of a Motrin[®] tablet (DTHS files).

---- marks the date that a product was granted OTC status.

xxxx marks the effective date of regulation under the Poison Prevention Packaging Act (PPPA).

**Table 2. Reports of Accidental Ingestions of NSAIDs
(Children less than 5 years old, TESS, 1993-1995).**

	TOTAL	MINOR	MODERATE	MAJOR
Ketoprofen	250	12	0	0
OTC Naproxen	----- <i>189</i> 776	--- 7 29	-- 0 3	-- 0 0
Non-OTC Naproxen	1,413 <i>1,115</i> 676	53 <i>53</i> 19	2 <i>1</i> 3	0 <i>0</i> 0
OTC Ibuprofen	9,215 <i>9,028</i> 8,240	278 <i>258</i> 226	12 <i>12</i> 8	1 <i>1</i> 0
Rx Ibuprofen	3,558 <i>4,011</i> 6,138	150 <i>126</i> 193	3 <i>6</i> 6	0 <i>0</i> 0
Unknown Ibuprofen	2,818 <i>2,954</i> 3,058	101 <i>101</i> 105	8 <i>5</i> 3	1 <i>1</i> 0
Other NSAIDs	2,912 <i>3,048</i> 2,573	138 <i>141</i> 117	3 <i>6</i> 4	1 <i>1</i> 0

Data in standard type refer to 1993; italicized data refer to 1994; bolded data refer to 1995. Ingestion refers to cases where the material enters the mouth, and includes ingestions accompanied by aspiration. **Minor Symptoms** - The patient exhibited some minimal signs or symptoms which resolved rapidly. **Moderate Symptoms** - The patient exhibited signs or symptoms that were more pronounced, prolonged, or of a systemic nature which usually required some form of treatment. Symptoms were not life threatening and the patient returned to a pre-exposure state of well-being with no residual disability or disfigurement. **Major Symptoms** - The patient exhibited some symptoms which were life-threatening or resulted in disfigurement or residual disability.

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United States
CONSUMER PRODUCT SAFETY COMMISSION
Washington, D.C. 20207

MEMORANDUM

DATE: February 18, 1997

TO : Jacqueline N. Ferrante, Ph.D.,
Project Manager, Ketoprofen

Through: Warren J. Prunella, AED, EC *W/PS*

FROM : Marcia P. Robins, ^{mpr}EC
(504-0962 x 1329)

SUBJECT: Final Rule for Child-Resistant Packaging for Over-the-Counter Packages Containing More Than 50 mgs
Ketoprofen: Regulatory Flexibility Issues

The Regulatory Flexibility Act (RFA [PL 96-345]) generally requires agencies to prepare and make available for public comment an initial regulatory flexibility analysis describing the impact of the rule on small businesses and other small entities, when a general notice of proposed rulemaking is published in the *Federal Register*. However, under section 605, no such analysis is required if the Commission certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. In its proposal to require child-resistant (CR) packaging for over-the-counter (OTC) ketoprofen preparations containing greater than 50 mg ketoprofen per package (November 20, 1996) the Commission certified under section 605 of the RFA that the proposal was not expected to have a significant economic effect on a substantial number of small businesses or other small entities. The determination was based on the following information.

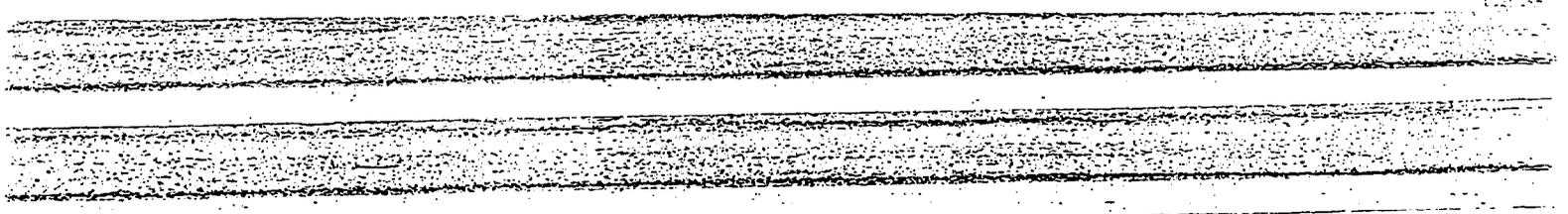
A requirement that OTC ketoprofen preparations meet Poison Prevention Packaging Act (PPPA) standards will not affect the two companies (neither of which are small) with marketing approval for OTC ketoprofen. One marketer is voluntarily using CR packaging on all three of its package sizes; the other marketer is voluntarily using CR packaging on two of its three package sizes. PPPA standards permit the marketing of OTC preparations in one non-CR package size for easier access by physically challenged persons. Companies that choose to enter the ketoprofen market in the future would incur no incremental costs for CR packaging since their products would not have been marketed in non-CR packages. Further, since CR closures are readily available at low incremental costs, their costs would not

be an entry barrier for future small business marketers. In addition, there are no recordkeeping or reporting requirements under the PPPA.

The RFA requires a final regulatory flexibility analysis when an agency issues a final rule unless the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. The public comments on the proposed rule provided no additional information regarding potential adverse impacts on small businesses or other small entities. Based on all of the economic information available on the proposed rule, the Directorate for Economic Analysis concludes that the final action to require CR packaging for OTC drug preparations containing greater than 50 mg ketoprofen in a single package will not have a significant economic effect on a substantial number of small entities.



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UNITED STATES GOVERNMENT
MEMORANDUM

U.S. CONSUMER PRODUCT
SAFETY COMMISSION
WASHINGTON, D.C. 20207
FEB 27 1997

TO: Jacqueline N. Ferrante, Ph.D., Manager, Ketoprofen,
Epidemiology & Health Sciences

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director
for Epidemiology & Health Sciences *mad*

Marilyn L. Wind, Ph.D., Director, Division of Poison *MLW*
Prevention and Scientific Coordination, Directorate
for Epidemiology & Health Sciences

FROM: Charles Wilbur, Consumer Safety Officer *gw*
Division of Poison Prevention and Scientific
Coordination, Directorate for Epidemiology & Health
Sciences, (504-0477, ext. 1204)

Tewabe Asebe, Industrial Engineer *T.A.*
Division of Poison Prevention and Scientific
Coordination, Directorate for Epidemiology & Health
Sciences, (504-0477, ext. 1379)

SUBJECT: Technical Feasibility, Practicability, and
Appropriateness Determination for the Final Rule to
Require Child-Resistant Packaging for OTC Products
Containing Ketoprofen.

The attached evaluation summarizes the Epidemiology &
Health Sciences determinations of technical feasibility,
practicability, and appropriateness for the final rule for over-
the-counter (OTC) products containing ketoprofen.

PPPA
FINAL RULE
OTC KETOPROFEN
TECHNICAL FEASIBILITY,
PRACTICABILITY,
AND
APPROPRIATENESS
Charles J. Wilbur
Tewabe Asebe
FEBRUARY 1997



DIRECTORATE FOR EPIDEMIOLOGY & HEALTH SCIENCES

DIVISION OF POISON PREVENTION
AND SCIENTIFIC COORDINATION

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SUMMARY

Epidemiology and Health Sciences concludes that findings can be supported that child-resistant packaging (CRP) requirements for OTC products containing ketoprofen are technically feasible (can be produced), practicable (lends itself to techniques of mass production), and appropriate (compatible with the substances contained within the package), for the following.

Products using continuous threaded and snap type reclosable packaging.

An effective date of 180 days is adequate as the two known manufacturers are using senior friendly special packaging designs.

Product using pouch packaging (unit dose).

An effective date of 180 days is adequate as the one manufacturer is using a child-resistant (CR) pouch (sampler) package which provides a senior friendly scissors opening option.

INTRODUCTION

To require that OTC ketoprofen products be packaged in CRP the Commission must find that CRP is:

- o Technically Feasible - Technology exists to produce packaging conforming to the standards.

- o Practicable - Special packaging complying with the standards, can be produced using modern mass production and assembly line techniques.

- o Appropriate - Packaging complying with the standards, adequately protects the integrity of the substance and does not interfere with its intended storage or use.

TECHNICAL FEASIBILITY

Most OTC ketoprofen containing products are packaged in various sizes of bottles with CR continuous threaded and snap type packaging¹. One product is packaged in unit dose CR pouch type packaging^{2,3,4,5}.

Various types and designs of senior friendly CR packaging can be obtained, see ASTM D3475, Standard Classification of Child-Resistant Packages⁶. Each type of packaging is addressed below.

CONTINUOUS THREADED RECLOSABLE PACKAGING: One manufacturer is presently using a senior friendly ASTM IA design package⁷. In addition various designs of senior friendly continuous threaded (screw) type reclosable CR packaging are readily available. See ASTM type I for possible candidates.

SNAP RECLOSABLE PACKAGING: One manufacturer is presently using a senior friendly ASTM IIIA design package⁸. Various designs of senior friendly continuous snap type reclosable CR packaging are readily available. See ASTM type III for possible candidates.

POUCH NON-RECLOSABLE PACKAGING: One manufacturer is presently using a CR pouch type unit dose packaging that has optional senior friendly scissors opening instructions on the label. See special packaging for Unit Non-Reclosable Packaging-ASTM IV type, Flexible (Strip/Pouch) packaging for other possible candidates.

The staff believes that data support the finding that special packaging for OTC ketoprofen containing products that require CR continuous threaded (screw), snap and unit dose pouch packaging are technically feasible.

PRACTICABILITY

Information is available to support the finding that the special packaging of OTC ketoprofen containing products is practicable.

CONTINUOUS THREADED AND SNAP RECLOSABLE PACKAGING: The two known companies producing ketoprofen are currently using CR packaging. Therefore, no changes are necessary to assembly line and mass production techniques in the manufacturing process. This shows that it is practicable to package OTC ketoprofen containing products in special packaging. No major problems are anticipated in using CR packaging from the manufacturing standpoint. The staff can, with available information, support the findings of practicability for continuous threaded and snap reclosable CR packaging.

POUCH NON-RECLOSABLE PACKAGING: One known manufacturer is using a CR pouch. No changes are necessary to assembly line and mass production techniques in the manufacturing process. This shows that it is practicable to package OTC ketoprofen containing products in pouch special packaging. No major problems are anticipated in using CR packaging from the manufacturing standpoint. The staff can, with available information, support the findings of practicability for unit dose pouch type CR packaging.

APPROPRIATENESS

Information is available to support the finding that the special packaging of OTC ketoprofen containing products is appropriate.

CONTINUOUS THREADED AND SNAP RECLOSABLE PACKAGING: Two OTC manufacturers are presently using special packaging. Therefore, shelf-life and integrity would not be expected to change. The materials for CRP are not detrimental to the integrity of the substance and do not interfere with its storage or use.

POUCH NON-RECLOSABLE PACKAGING: One OTC manufacturer is presently using special packaging. In this case shelf-life and integrity would not be expected to change. Other companies can utilize existing CR pouch designs and materials that are not detrimental to the integrity of the substance and will not interfere with its storage or use.

Staff, therefore, believe that the data support the finding that special packaging for OTC ketoprofen containing products are appropriate.

EFFECTIVE DATE

An effective date of 180 days is reasonable for continuous threaded and snap reclosable packaging. The two known companies marketing OTC ketoprofen products are presently using special packaging and would not require any changes to their production lines. The CRP suppliers have the requisite molds, assembly equipment, lining material and plastic resins to supply the required CRP quantities for this product. Adequate supplies of CRP for this product are available from the packaging manufacturer.

An effective date of 180 days appears adequate for companies who wish to use unit dose, CR pouch packaging. One known company marketing OTC ketoprofen products is presently using CR pouch packaging. Equipment and CR packaging material supplies for CR pouch packaging are available from various manufacturers.

CONCLUSION

The staff concludes that the findings can be supported that special packaging for OTC ketoprofen products are technically feasible, practicable, and appropriate for the following:

Products using continuous threaded, snap reclosable and pouch (unit-dose) packaging have available adequate supplies of the new senior friendly CRP to support an effective date of 180 days.

REFERENCES

1. Rice, Thomas F., President, Physicians' Desk Reference for Nonprescription Drugs, Medical Economics Co, Montvale, NJ 07645-1742, PDR, Edition 17, 1996, pp. 309, 503, 608, 528, 842.
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3. Rice, Thomas F., President, Physicians' Desk Reference, Medical Economics Co, Montvale, NJ 07645-1742, PDR, Edition 50, 1996, pp. 124 (Index), 340, 2767-2770, 667, 1426, 2679.
4. Asebe, Tewabe, Personal Communication, Product Manufacturer; Memo Record, Form 247, August 12, 1996. {CONFIDENTIAL}
5. Asebe, Tewabe, Wilbur, Charles, J., Laboratory Report, Form 221, CR Pouch, 1-3/4 x 2", ASTM IV A/C, 2 caplet, 96-400-8178, No. 2337, CPSC, Epidemiology & Health Sciences, August 23, 1996. {CONFIDENTIAL}
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7. Asebe, Tewabe, Wilbur, Charles, J., Laboratory Report, Form 221, CR Continuous Threaded Cap 28mm ASTM IA on a Plastic Bottle, 24 tablet, 96-400-8162, No. 2319, CPSC, Epidemiology & Health Sciences, August 6, 1996. {CONFIDENTIAL}
8. Asebe, Tewabe, Wilbur, Charles, J., Laboratory Report, Form 221, CR Snap Cap 28mm ASTM IIIA on a Plastic Bottle, 24 tablet, 96-400-7158, No. 2307, CPSC, Epidemiology & Health Sciences, July, 24, 1996. {CONFIDENTIAL}

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CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

Final Rule: Requirements for Child-Resistant Packaging;
Packages Containing More Than 50 mg of Ketoprofen

DRAFT 4/30/97

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

SUMMARY: The Commission is issuing a rule to require child-resistant packaging for ketoprofen preparations containing more than 50 mg of ketoprofen per retail package. Ketoprofen is a nonsteroidal anti-inflammatory drug and is used to relieve minor aches and pains and to reduce fever. The Commission has determined that child-resistant packaging is necessary to protect children under five years of age from serious personal injury and serious illness resulting from ingesting ketoprofen. The Commission takes this action under the authority of the Poison Prevention Packaging Act of 1970.

DATE: The rule will become effective on _____, 1997 [insert date that is 180 days after publication in the **FEDERAL REGISTER**] and applies to ketoprofen preparations packaged on or after that date.

FOR FURTHER INFORMATION CONTACT: Michael Bogumill, Division of Regulatory Management, Consumer Product Safety Commission, Washington, D.C. 20207; telephone (301) 504-0400 ext. 1368.

SUPPLEMENTARY INFORMATION:

A. Background

1. Relevant Statutory and Regulatory Provisions

The Poison Prevention Packaging Act of 1970 ("PPPA"), 15 U.S.C. 1471-1476, authorizes the Commission to establish standards for the "special packaging" of any household substance if (1) the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance and (2) the special packaging is technically feasible, practicable, and appropriate for such substance.

Special packaging, also referred to as "child-resistant (CR) packaging," is packaging that (1) is designed or constructed to be significantly difficult for children under five years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and (2) is not difficult for "normal adults" to use properly. 15 U.S.C. 1471(4). Household substances for which the Commission may require CR packaging include (among other categories) foods, drugs, or cosmetics as these terms are defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321). 15 U.S.C. 1471(2)(B). The Commission has performance requirements for special packaging. 16 CFR 1700.15, 1700.20.

Section 4(a) of the PPPA, 15 U.S.C. 1473(a), allows the manufacturer or packer to package a nonprescription product subject to special packaging standards in one size of non-CR packaging only if the manufacturer (or packer) also supplies the substance in CR packages of a popular size, and the non-CR packages bear conspicuous labeling stating: "This package for households without young children." 15 U.S.C. 1473(a), 16 CFR 1700.5.

2. Ketoprofen

Ketoprofen is a nonsteroidal anti-inflammatory drug ("NSAID"). This class of compounds also includes ibuprofen and naproxen. Ketoprofen is used to relieve minor aches and pains such as those associated with colds, toothaches, menstrual cramps, and muscular aches. It is also used to reduce fever.[1, 2]¹ For the past ten years, ketoprofen has been a prescription drug. Like most prescription drugs, it was required to be in CR packaging by the Commission's regulation of human oral prescription drugs, 16 CFR 1700.14(a)(10). The U.S. patent on ketoprofen expired in 1993. On October 6, 1995, the Food and Drug Administration ("FDA") granted nonprescription ("over-the-counter" or "OTC") status to ketoprofen.[2]

The OTC formulations, ketoprofen and ketoprofen tartrazine, contain 12.5 milligrams (mg) of ketoprofen per dose. The

¹ Numbers in brackets refer to documents listed at the end of this notice.

recommended dose is one tablet every four to six hours. The maximum daily dose is six tablets.[2]

3. Special Packaging

The current marketers are voluntarily placing ketoprofen in CR packaging. However, a mandatory special packaging standard for ketoprofen products will ensure that other companies that may market such products in the future would use CR packaging.

Two other NSAIDs that previously became available OTC are ibuprofen and naproxen. After ibuprofen was introduced OTC, there was an increased incidence of accidental ingestions of the drug by children under five.[2]

In part to avoid a similar experience with naproxen, in 1995, the Commission then issued a rule requiring CR packaging for naproxen preparations containing 250 mg or more per retail package. 60 Fed. Reg. 38671. The rule became effective February 6, 1996. Similar reasoning applies to ketoprofen.

A mandatory standard for ketoprofen will also enable the Commission to ensure that its packaging meets the performance requirements of the PPPA test protocol set forth at 16 CFR 1700.15; 1700.20.

4. The Proposed Rule

On November 20, 1996, the Commission issued a notice of proposed rulemaking ("NPR") that would require CR packaging for OTC drugs containing more than 50 mg of ketoprofen. 61 FR 59043. The Commission received only one comment, from the American Society of Health-System Pharmacists, in response to the proposed

rule.[6] That comment expressed support for the proposed rule, stating that the toxicity data demonstrate that ketoprofen can cause serious illness and injury to children and that the proposed rule was consistent with packaging rules for other NSAIDs.

B. Toxicity of Ketoprofen

As explained in the NPR, the Commission's Directorate for Epidemiology and Health Sciences reviewed the toxicity of ketoprofen. Side effects commonly associated with ketoprofen, as with other NSAID's, are gastrointestinal (GI) complications, such as nausea, vomiting, diarrhea, constipation, heartburn, and abdominal pain. Other common adverse effects include headache, dizziness, visual disturbances, rash, and hypersensitivity reactions.[2]

Ketoprofen may also cause more severe adverse GI effects, such as gastric or duodenal ulcers with bleeding or perforation; intestinal ulcers; ulcerative stomatitis or colitis; gingival ulcers; perforation and hemorrhage of the esophagus, stomach, small or large intestine; hematemesis; and rectal bleeding. Renal injuries also may result from chronic use of ketoprofen.[2]

The staff reviewed the relevant medical literature which cites several cases of severe adverse reactions to ketoprofen administration and ketoprofen overdoses.[2] The NPR provides details of some of these cases. 61 FR 59044-45.

The FDA maintains a data base known as the Adverse Events Reporting System ("AERS") for reports of adverse reactions

detected after marketing a drug or biological product. Drug manufacturers are required to report to the FDA any known adverse effects associated with their products.

Of the 903 ketoprofen-associated cases reported to the FDA between 1986 and October 1995, the most common adverse reactions were abdominal pain (122), diarrhea (87), nausea (82), GI hemorrhage (70), rash (55), indigestion (39), labored breathing (34), allergic reaction (30), dizziness (30), and hives (30). Among the ketoprofen cases in the AERS database are 51 more serious reactions, i.e., hospitalizations, reactions resulting in permanent disability, or deaths. Five of these involved children under 16 years of age.[2]

The staff reviewed accidental ingestion data for children under age five. The American Association of Poison Control Center ("AAPCC") collects incident data through its Toxic Exposure Surveillance System ("TESS"). Poisoning incidents involving ketoprofen from 1985 to 1994 were not recorded separately from other NSAIDs unless they were fatal. No deaths involving ketoprofen were reported during this period.[2] In 1995, CPSC staff requested a separate report on ketoprofen. This report showed 250 accidental ingestions of ketoprofen involving children under five years old in 1995. Twelve of these incidents resulted in minor outcomes.[8]

CPSC's data base, the National Electronic Injury Surveillance System ("NEISS") monitors emergency room visits to selected hospitals throughout the United States. As stated in

the NPR, review of NEISS data from 1988 to June 1996 showed three cases involving ketoprofen and children under five years old. All three incidents occurred in 1996. None were fatal or required hospitalization.[2] Since publication of the NPR, seven new cases of children ingesting ketoprofen were reported through NEISS.[8]

C. Level for Regulation

This rule requires special packaging for OTC ketoprofen products containing more than 50 mg ketoprofen per retail package, the same level as proposed in the NPR. This level is based on established guidelines for medical treatment following pediatric ingestion of NSAIDs.[5] These guidelines suggest medical treatment for young children who ingest five times the maximum single therapeutic dose. For ketoprofen, the maximum single therapeutic dose is 75 mg or 1.08 mg/kg assuming an average adult weight of 70 kg. The dose of ketoprofen requiring medical intervention would be five times 1.08 mg/kg, which in a 10-kg child would be more than 50 mg of ketoprofen, or four OTC tablets.[2]

D. Statutory Considerations

1. Hazard to Children

As noted above and in the NPR, the toxicity data concerning children's ingestion of ketoprofen demonstrate that this compound can cause serious illness and injury to children. Moreover, the preparations are readily available to children. The Commission concludes that a regulation is needed to ensure that products

subject to the regulation will be placed in CR packaging. The regulation will enable the Commission to enforce the CR packaging requirement and ensure that effective CR packaging is used.

Pursuant to section 3(a) of the PPPA, 15 U.S.C. 1472(a), the Commission finds that the degree and nature of the hazard to children from ingesting ketoprofen is such that special packaging is required to protect children from serious illness. The Commission bases this finding on the toxic nature of these products, described above, and their accessibility to children in the home.

2. Technical Feasibility, Practicability, and Appropriateness

In issuing a standard for special packaging under the PPPA, the Commission is required to find that the special packaging is "technically feasible, practicable, and appropriate." 15 U.S.C. 1472(a)(2). Technical feasibility may be found when technology exists or can be readily developed and implemented by the effective date to produce packaging that conforms to the standards. Practicability means that special packaging complying with the standards can utilize modern mass production and assembly line techniques. Packaging is appropriate when it will adequately protect the integrity of the substance and not interfere with the substance's intended storage or use. [4, 10]

The current marketers of OTC ketoprofen voluntarily use CR packaging. Similar designs have been shown to meet the revised testing protocol for senior adult use effectiveness. Therefore,

the Commission concludes that CR packaging for ketoprofen is technically feasible, practicable, and appropriate. [3, 4, 10]

3. Other Considerations

In establishing a special packaging standard under the PPPA, the Commission must consider the following:

- a. The reasonableness of the standard;
- b. Available scientific, medical, and engineering data concerning special packaging and concerning childhood accidental ingestions, illness, and injury caused by household substances;
- c. The manufacturing practices of industries affected by the PPPA; and
- d. The nature and use of the household substance. 15 U.S.C. 1472(b).

The Commission has considered these factors with respect to the various determinations made in this notice, and finds no reason to conclude that the rule is unreasonable or otherwise inappropriate.

E. Effective Date

The PPPA provides that no regulation shall take effect sooner than 180 days or later than one year from the date such final regulation is issued, except that, for good cause, the Commission may establish an earlier effective date if it determines an earlier date to be in the public interest. 15 U.S.C. 1471n.

The Commission does not believe that a shorter effective date is necessary to protect the public interest. The companies

that are currently marketing ketoprofen are voluntarily using CR packaging. The Commission does not have any indication that quantities of ketoprofen will be marketed in non-CR packaging before a 180-day effective date, other than in a single size non-CR package, as allowed under the PPPA. Thus, the Commission finds that a 180-day effective date is consistent with the public interest. Accordingly, this rule will take effect 180 days after its publication in the Federal Register and will apply to products that are packaged on or after the effective date.

F. Regulatory Flexibility Act Certification

When an agency undertakes a rulemaking proceeding, the Regulatory Flexibility Act, 5 U.S.C. 601 *et seq.*, generally requires the agency to prepare proposed and final regulatory flexibility analyses describing the impact of the rule on small businesses and other small entities. Section 605 of the Act provides that an agency is not required to prepare a regulatory flexibility analysis if the head of an agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

When the Commission issued its proposed rule, the Commission's Directorate for Economic Analysis prepared a preliminary assessment of the impact of a rule to require special packaging for ketoprofen preparations with more than 50 mg ketoprofen in a single package.[3] Based on this assessment, the Commission concluded that such a requirement would not have a significant impact on a substantial number of small businesses or

other small entities because the current marketers of ketoprofen are using CR packaging and the relatively low costs of CR packaging should not be an entry burden for future marketers. The Commission received no comments on this determination and is aware of no information that would alter its determination.[9] Therefore, the Commission certifies that this rule would not have a significant impact on a substantial number of small businesses or other small entities.

G. Environmental Considerations

Pursuant to the National Environmental Policy Act, and in accordance with the Council on Environmental Quality regulations and CPSC procedures for environmental review, the Commission assessed the possible environmental effects associated with the proposed PPPA requirements for ketoprofen preparations.

The Commission's regulations state that rules requiring special packaging for consumer products normally have little or no potential for affecting the human environment. 16 CFR 1021.5(c)(3). Therefore, as stated in the proposed rule, because the rule would have no adverse effect on the environment, neither an environmental assessment nor an environmental impact statement is required.[3]

H. Preemption

According to Executive Order 12988 (February 5, 1996), agencies must state in clear language the preemptive effect, if any, of new regulations.

The PPPA provides that, generally, when a special packaging standard issued under the PPPA is in effect, "no State or political subdivision thereof shall have any authority either to establish or continue in effect, with respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard." 15 U.S.C. 1476(a). A State or local standard may be excepted from this preemptive effect if (1) the State or local standard provides a higher degree of protection from the risk of injury or illness than the PPPA standard; and (2) the State or political subdivision applies to the Commission for an exemption from the PPPA's preemption clause and the Commission grants the exemption through a process specified at 16 CFR Part 1061. 15 U.S.C. 1476(c)(1). Also, the Federal government, or a State or local government, may establish and continue in effect a non-identical special packaging requirement that provides a higher degree of protection than the PPPA requirement for a household substance for the Federal, State or local government's own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the rule requiring CR packaging for ketoprofen would preempt non-identical state or local special packaging standards for ketoprofen.

I. Other Executive Orders

The Commission certifies that the rule does not have sufficient implications for federalism to warrant a Federalism Assessment under Executive Order 12612 (October 26, 1987).

Independent regulatory agencies are encouraged, but not required, to comply with Executive Order 13045 (April 23, 1997). This rulemaking is not subject to that order because it is not a "covered agency action" as defined in the order and because the rulemaking was initiated before the order was issued. In any event, the Commission's discussion in this notice of the issues involved in the rulemaking comply with the order's requirements for an analysis of the rule and its environmental, health and safety effects on children.

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

For the reasons given above, 16 CFR part 1700 is amended as follows:

PART 1700-- [AMENDED]

1. The authority citation for part 1700 continues to read as follows:

Authority: Pub. L. 91-601, secs. 1-9, 84 Stat. 1670-74, 15 U.S.C. 1471-76. Secs 1700.1 and 1700.14 also issued under Pub. L. 92-573, sec. 30(a), 88 Stat. 1231. 15 U.S.C. 2079(a).

2. Section 1700.14 is amended by republishing paragraph (a) introductory text and adding new paragraph (a)(26) to read as follows:

§ 1700.14 Substances requiring special packaging.

(a) *Substances.* The Commission has determined that the degree or nature of the hazard to children in the availability of the following substances, by reason of their packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substances, and the special packaging herein required is technically feasible, practicable, and appropriate for these substances:

* * * * *

(26) *Ketoprofen.* Ketoprofen preparations for human use and containing more than 50 mg of ketoprofen in a single retail package shall be packaged in accordance with the provisions of § 1700.15(a), (b) and (c).

Dated: _____

Sadye E. Dunn,
Secretary, Consumer Product Safety Commission

List of Relevant Documents

(Note. This list of relevant documents will not be printed in the Code of Federal Regulations.)

1. Briefing memorandum from Jacqueline Ferrante, Ph.D., HSPS, to the Commission, "Proposed Rule to Require Child-Resistant Packaging for Ketoprofen," October 15, 1996.

2. Memorandum from Susan C. Aitken, Ph.D., HSHE, to Jacqueline Ferrante, Ph.D., HSPS, "Toxicity of Ketoprofen," August 19, 1996.

3. Memorandum from Marcia P. Robins, EC, to Jacqueline Ferrante, Ph.D., HSPS, "Preliminary Assessment of Economic and Environmental Effects of a Proposal to Require Child-Resistant Packaging for OTC Pharmaceuticals Containing Ketoprofen," August 19, 1996.

4. Memorandum from Charles Wilbur, HSPS, to Jacqueline Ferrante, Ph.D., HSPS, "Technical Feasibility, Practicability, and Appropriateness Determination for the Proposed Rule to Require Child-Resistant Packaging for OTC Products Containing Ketoprofen," August 20, 1996.

5. Vale, J.S. and Meredith, T.J., Acute Poisoning Due to Non-steroidal Anti-inflammatory Drugs: Clinical Features and Management. Med. Toxicol. 1:12-31, 1986.

6. Letter from Gary C. Stein, Ph.D., Senior Government Affairs Associate, American Society of Health-System Pharmacists, to Office of the Secretary, CPSC, dated January 30, 1997.

7. Briefing memorandum from Jacqueline Ferrante, Ph.D., HSPS, to the Commission, "Final Rule to Require Child-Resistant Packaging for Ketoprofen," May 5, 1997.

8. Memorandum from Susan C. Aitken, Ph.D., HSHE, to Jacqueline Ferrante, Ph.D., HSPS, "Update of Injuries to Accidental Ingestion of Ketoprofen Products," March 4, 1997.

9. Memorandum from Marcia P. Robins, EC, to Jacqueline Ferrante, Ph.D., HSPS, "Final Rule for Child-Resistant Packaging for OTC Packages Containing More than 50 mgs Ketoprofen: Regulatory Flexibility Issues," February 18, 1997.

10. Memorandum from Charles Wilbur, HSPS, to Jacqueline Ferrante, Ph.D., HSPS, "Technical Feasibility, Practicability, and Appropriateness Determination for the Final Rule to Require Child-Resistant Packaging for OTC Products Containing Ketoprofen," February 27, 1997.