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Department of Health and Human Services

Food and Drug Administration

21 CFR Part 201

Warning Statements Required for Over-
the-Counter Drugs Containing Water-
Soluble Gums as Active Ingredients;
Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 90N-0200]

RIN 0905-AA06

Warning Statements Required for Over-the-Counter Drugs Containing Water-Soluble Gums as Active Ingredients

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking requiring a warning in the labeling of all over-the-counter (OTC) drug products containing as active ingredients water-soluble gums, e.g., guar gum, karaya gum, plantago seed (psyllium), tragacanth, and xanthan gum. This warning would alert users of these products to consume adequate fluid and to avoid using such products if the person has previously experienced any difficulty in swallowing. FDA is issuing this notice of proposed rulemaking after receiving reports of esophageal obstruction and asphyxiation involving OTC drug products containing water-soluble gums as active ingredients. Water-soluble gums are used primarily in OTC laxative and weight control drug products. These ingredients are under review in the ongoing rulemakings for OTC laxative and weight control drug products as part of FDA's OTC drug review. FDA has determined that implementation of a warning for these ingredients should not await completion of the OTC drug review process. Therefore, a warning is being proposed now to support the safe use of OTC drug products containing water-soluble gums. The proposed warning will be incorporated into the pertinent OTC drug monographs as the rulemakings for these drug products are completed.

DATES: Written comments, objections, or requests for oral hearing on the proposed rulemaking before the Commissioner of Food and Drugs by December 31, 1990. Written comments on the agency's economic impact determination by December 31, 1990.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-82, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug

Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: FDA is proposing to amend 21 CFR part 201, Subpart G, *Specific Labeling Requirements for Specific Drug Products*, to include a warning for all OTC drug products containing water-soluble gums as active ingredients. The warning would state: (Select one of the following, as appropriate: "Take" or "Mix") "this product with at least 8 ounces (a full glass) of water or other fluid. Taking this product without adequate fluid may cause it to swell and block your throat or esophagus and may cause choking. Do not take this product if you have ever had difficulty in swallowing or have any throat problems. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention." The agency considers this warning necessary because water-soluble gums used as active ingredients in certain orally-administered OTC drug products have been associated with esophageal obstruction and asphyxiation.

Water-soluble gums are primarily used in OTC bulk laxative and weight control drug products. The ingredients involved are natural or semisynthetic hydrocolloid gums including, but not limited to, agar, alginate acid, carboxymethylcellulose sodium, carrageenan, glucomannan,¹ guar gum, karaya gum, kelp,² methylcellulose, plantago seed (psyllium),³ polycarbophil, tragacanth, and xanthan gum. The ingredients polycarbophil and polycarbophil calcium are also used in OTC antidiarrheal drug products.

Because of the hydrophilic nature of water-soluble gums, when water is added to the gum it swells and increases in bulk. If inadequate water is added, a viscous, semi-solid mass forms. The rate and degree of swelling, as well as the viscosity and adhesiveness of the mass, vary from product to product depending

¹ Glucomannan is the commonly used name for the glucose/mannose polymer (B-1.4 linked) polymannose acetate.

² The panel that evaluated this ingredient as part of FDA's OTC drug review designated it "sea kelp." However, "kelp" is the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1990."

³ The panel that evaluated the ingredients "plantago ovata husks, plantago seeds, psyllium hemicellulose, psyllium hydrophilic mucilloid, psyllium seed, and psyllium seed husks" as part of FDA's OTC drug review designated these ingredients as "psyllium." However, "plantago seed" is the official name for these ingredients in the "USAN and the USP dictionary of drug names, 1990."

on the amount of gum present. When orally-administered OTC drug products containing a high level of one of these gums are used by individuals who have difficulty in swallowing, or when such products are taken with an inadequate amount of water or other fluid, there is a risk that the product will swell and form a viscous adhesive mass that can block the throat or esophagus. The type and degree of adverse effects are influenced by the amount of fluid taken with the product.

Esophageal obstruction and asphyxiation associated with the ingestion of water-soluble gums have been reported in the literature since the 1930's, although such reports were relatively rare. However, in recent years FDA has become aware of an increased number of reports. FDA is aware of at least 113 cases of esophageal obstruction and 4 cases of asphyxia associated with orally-administered OTC laxative and weight control products containing these ingredients. Death occurred in six of these cases.

I. Background

As part of FDA's OTC drug review, water-soluble gums were reviewed as OTC bulk laxatives by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic and Antiemetic Drug Products (Laxative Panel) and as OTC weight control drug products by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel).

The Laxative Panel, in its report published in the *Federal Register* of March 21, 1975 (40 FR 12902), classified five water-soluble gums in Category I (safe and effective)—carboxymethylcellulose sodium, karaya gum, methylcellulose, polycarbophil, and psyllium. Three additional water-soluble gums were classified in Category III (insufficient effectiveness data)—agar, carrageenan, and guar gum. In its discussion of these bulk laxative ingredients, the Laxative Panel acknowledged the risk of esophageal obstruction from water-soluble gums (40 FR 12902 at 12907) and specifically noted with respect to psyllium:

Esophageal, gastric, small intestinal and rectal obstruction due to accumulation of mucilaginous derivatives of psyllium preparations have been described on several occasions. The common denominator in most cases has been insufficient water intake or underlying organic disease which resulted in compromise of the intestinal lumen. (40 FR 12903).

The Laxative Panel recommended that labeling for bulk laxative ingredients stress the importance of adequate fluid

intake, i.e., 8 ounces (oz) of liquid, with each dose.

After reviewing the recommendations of the Laxative Panel and considering public comments received following publication of its report, FDA published a tentative final monograph on OTC laxative drug products in the *Federal Register* of January 15, 1985 (50 FR 2124). The risk of esophageal obstruction from certain bulk laxative ingredients, including water-soluble gums, and the need for adequate fluid intake (8 oz) with each dose of these ingredients was again discussed in comments 36 and 37 of the tentative final monograph (50 FR 2124 at 2131 and 2132).

In an amendment to the tentative final monograph on OTC laxative drug products, published in the *Federal Register* of October 1, 1986 (51 FR 35136), FDA proposed that bulk laxative ingredients be administered in divided doses rather than a single daily dose. This action was taken because it was noted that: " * * * the maximum daily dose of some bulk laxatives is so large that it may pose a risk of esophageal obstruction if taken at one time." (51 FR 35136). In response to these proposals, a major manufacturer of psyllium-containing bulk laxatives commented in support of the FDA's recommendation regarding adequate fluid intake (8 oz) with each dose of a bulk laxative. This manufacturer recommended that all bulk laxatives bear the following warning (Ref. 1):

Bulk forming agents have the potential to block the esophagus, particularly in the presence of esophageal narrowing or when consumed with insufficient fluid. Patients with esophageal narrowing should not use this product. If you observe symptoms of esophageal blockage, including chest pain/pressure, regurgitation and difficulty swallowing, seek immediate medical attention.

The Miscellaneous Internal Panel, in its report on OTC weight control drug products published in the *Federal Register* of February 26, 1982 (47 FR 8466), classified the water-soluble gums alginic acid, carboxymethylcellulose sodium, carrageenin, chondrus,⁴ guar gum, karaya gum, methylcellulose, psyllium, sea kelp, and xanthan gum in Category III. The Miscellaneous Internal Panel noted, with respect to carboxymethylcellulose sodium and methylcellulose, that occasional cases of esophageal obstruction have occurred when these ingredients are chewed or swallowed without liquid (47 FR 8466 at

8477 and 8478). While concluding that the water-soluble gums listed above are safe, the Miscellaneous Internal Panel recommended that directions for these products state: "Take a full glass of water (8 ounces) with each dose." (47 FR 8477 to 8479).

II. Adverse Reactions Associated With Water-Soluble Gums

During 1984 and 1985, 7 cases of esophageal obstruction caused by the swelling of tablets containing glucomannan were reported to the Australian Adverse Drug Reactions Advisory Committee (Ref. 2). All of the subjects were women between the ages of 18 and 62 years who were taking glucomannan-containing products for weight control. None had esophageal disease. Obstruction was complete in 5 of the 7 cases. In all but one case the obstruction was caused by a swollen mass resulting from a single tablet. Esophagoscopy was needed to remove the obstruction in 5 cases. One subject suffered esophageal perforation requiring hospitalization for 2 months (Ref. 2).

FDA's spontaneous reporting system has recently received 17 reports of esophageal obstruction (16 between June 1988 and August 1989) resulting from the use of one of these drug products (Ref. 3). The product contained 500 milligrams (mg) guar gum per tablet, with directions to start with 4 tablets 30 minutes before each meal on the first day and to increase up to 10 tablets 30 minutes before each meal on the 15th day and thereafter. This dosage regimen eventually results in a maximum dose of 15 grams (g) of guar gum per day. Ten of the cases of esophageal obstruction required hospitalization, and one person eventually died as an indirect result of the obstruction. This person developed massive pulmonary emboli one week after open chest surgery to repair an esophageal tear sustained during removal of the guar gum obstruction.

This potential for esophageal obstruction represents a serious hazard for an OTC drug, and the 17 cases are presumed to represent a substantial underreporting. OTC drugs of this type, i.e., those without approved applications, are not subject to mandatory reporting requirements, and reports such as the above 17, which were voluntarily submitted by health professionals, normally account for only about 10 percent of all reports in the agency's spontaneous reporting system.

There has also been a report in the literature of an esophageal obstruction resulting from another guar gum product, this one composed of guar gum and grapefruit fiber (Ref. 4). In that case, a

middle-aged man was unable to eat or drink for 12 hours after taking one weight control tablet composed of an unspecified amount of guar gum and grapefruit fiber. Endoscopy revealed a soft, fibrous mass impacted in the esophagus; it was broken apart by the endoscope. The agency is also aware of a report in which a 63-year-old diabetic suffered an esophageal obstruction after taking an OTC product containing guar gum. The obstruction required removal with biopsy tongs (Ref. 5). In another report, a 59-year-old male suffered esophageal obstruction after taking a product containing guar gum (Ref. 6). Esophagoscopy was required to remove the obstruction.

Between 1975 and 1989, FDA received 61 adverse reaction reports of esophageal obstruction from OTC laxative drug products containing a high concentration of psyllium (Ref. 7). These cases involved subjects ranging in age from 8½ months to 85 years. In at least 4 of the 61 cases, inadequate amounts of fluid were administered with the products. In 13 of the cases, there was evidence of esophageal narrowing or swallowing dysfunction. Death due to asphyxia occurred in 4 cases.

The agency is also aware of reports in which 3 individuals between 56 and 75 years of age suffered esophageal obstruction after taking a psyllium-containing laxative with "a few sips" or "a single swallow" of water. In two of these cases, esophagoscopy was required to remove the obstruction (Refs. 8, 9, and 10).

Noble and Grannis (Ref. 11) report the case of an 81-year-old male, with a history of swallowing dysfunction, who suffered an esophageal obstruction after taking a psyllium-containing laxative with an inadequate amount of water. He required esophagoscopy to remove the mass. The authors mention 21 episodes of esophageal obstruction due to this particular laxative product within a 3-year period.

The agency is aware of two reports of esophageal obstruction from OTC drug products containing karaya gum. In one case, a 76-year-old woman experienced an obstruction that had to be removed by a Foley catheter (Ref. 12). In the second case, an 80-year-old woman died from an esophageal obstruction after taking an OTC laxative drug product with an inadequate amount of water (Ref. 13).

The agency is also aware of one case of esophageal obstruction resulting from a methylcellulose-containing laxative. A 42-year-old woman suffered an obstruction after taking a methylcellulose-containing laxative with

⁴ Chondrus was classified in Category III as a separate ingredient by the Miscellaneous Internal Panel, however, chondrus is but one of several sources of carrageenin.

only a small sip of juice. The resulting obstruction had to be pushed downward into the stomach with a gastroscop (Ref. 14).

Although there is little, if any, current use in this country of OTC drug products containing tragacanth as an active ingredient, the agency is aware of two reports of esophageal obstruction that occurred a number of years ago from an OTC laxative drug product containing this ingredient (Refs. 15 and 16). A 59-year-old woman (Ref. 15) and a 47-year-old man (Ref. 16) suffered an obstruction following ingestion of the same product with a small amount of water. In both cases, esophagoscopy was necessary to remove the obstruction.

References

- (1) Comment No. C00100, Docket No. 78N-036L, Dockets Management Branch.
- (2) Henry, D.A., et al., "Glucomanan and Risk of Oesophageal Obstruction," *British Medical Journal*, 292: 391-392, 1986.
- (3) Adverse Drug Reaction Reports, Reference No. 3 in OTC Volume AF, Docket No. 90N-0200, Dockets Management Branch.
- (4) Gebhard, R.L., and J. Albrecht, "The Diet Pill that Worked," *The New England Journal of Medicine*, 322:702, 1990.
- (5) Ranft, K., and W. Imhof, "Bolusobstruktion des Distalen Oesophagus Durch Pflanzliche Quellstoffe (Guarmehl)," *Deutsche Medizinische Wochenschrift*, 108: 1. 68-1969, 1983.
- (6) Sorensen, A.J., and O.R. Rasmussen, "Synkestop Efter Indtagelse af Fiberholding Helsekostprodukt Lej-Guar," *Ugeskrift For Læger*, 145:171-172, 1983.
- (7) Adverse Drug Reaction Reports, Reference No. 7 in OTC Volume AF, Docket No. 90N-0200, Dockets Management Branch.
- (8) Hinkel, C.L., "Complete Obstruction of the Esophagus Following Serutan Ingestion," *Journal of the American Medical Association*, 146:1129-1131, 1951.
- (9) Roden, V., "Esophageal Obstruction Due to Serutan," *Journal of the American Medical Association*, 147:777, 1951.
- (10) Melamed, A., and A. Marek, "Esophageal Obstruction Due to Serutan," *Journal of the American Medical Association*, 152:318, 1953.
- (11) Noble, J.A., and F.W. Grannis, "Acute Esophageal Obstruction by a Psyllium-based Bulk Laxative," *Chest*, 86:800, 1984.
- (12) Vouchet, O., and A. Mouchet, "Obstruction de l'Œsophage Par Mucilage," *La Nouvelle Presse Medicale*, 3:1223-1225, 1974.
- (13) Sandeman, D.R., et al., "Oesophageal Obstruction Due to Hygroscopic Gum Laxative," *Lancet*, 1:364-365, 1980.
- (14) Roesch, W., and R. Ottenjann, "Impacted Methylcellulose—Foreign Body Simulating Esophageal Carcinoma," *Endoscopy*, 3:189-191, 1970.
- (15) Waltz, M.R., "Esophageal Obstruction Resulting From an Injudicious Method of Ingesting a Hygroscopic Gum Laxative (SARAKA)," *Journal of the American Medical Association*, 112:229, 1939.
- (16) Goldman, J.L., "Esophageal Obstruction From a Hygroscopic Gum Laxative (SARAKA)," *Journal of the American Medical Association*, 108:1408-1409, 1937.

III. The Agency's Conclusions on the Safety of Water-Soluble Gums in Orally-Administered OTC Drug Products

The Safety and proper labeling of water-soluble gums in orally-administered OTC drug products is being considered as part of FDA's ongoing review of all OTC drugs, specifically in the OTC laxative and weight control drug products rulemakings. However, these rulemakings are still pending.

Esophageal obstruction and asphyxiation due to orally-administered OTC drug products containing water-soluble gums, hydrophilic gums, and hydrophilic mucilloids as active ingredients are significant health risks when these products are taken without adequate fluid or when they are used by individuals with esophageal narrowing or dysfunction, or with difficulty in swallowing. Therefore, prior to completion of the OTC drug review, the agency is proposing to require a warning for all OTC drug products containing water-soluble gums, hydrophilic gums, or hydrophilic mucilloids as active ingredients. These ingredients include, but are not limited to, agar, alginic acid, carboxymethylcellulose sodium, carrageenan, chondrus, glucomanan, guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil, tragacanth, and xanthan gum. (NOTE: Although some of these ingredient names are no longer official, they do appear in the labeling of some products. Therefore, the agency is including all ingredient names, whether official or not, in the proposed regulation.)

Because of the potential serious health risk involved the agency is proposing that this warning appear in bold print and capital letters. The required warning would state the following:

WARNING: (Select one of the following, as appropriate: TAKE or MIX) THIS PRODUCT WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID TAKING THIS PRODUCT WITHOUT ADEQUATE FLUID MAY CAUSE IT TO SWELL AND BLOCK YOUR THROAT OR ESOPHAGUS AND MAY CAUSE CHOKING. DO NOT TAKE THIS PRODUCT IF YOU HAVE EVER HAD DIFFICULTY IN SWALLOWING OR HAVE ANY THROAT PROBLEMS

IF YOU EXPERIENCE CHEST PAIN, VOMITING, OR DIFFICULTY IN SWALLOWING OR BREATHING AFTER

TAKING THIS PRODUCT, SEEK IMMEDIATE MEDICAL ATTENTION.

This warning in § 201.319, which would be required on the effective date of a final rule, would eventually be incorporated into the labeling contained in the individual applicable OTC drug monographs (e.g., laxative drug products and weight control drug products) as they are finalized. However, it would be an unacceptable health risk to delay implementation until these rulemakings are completed. Manufacturers are encouraged to comply voluntarily with this proposed rule at the earliest possible date.

The agency has examined the regulatory impact and regulatory flexibility implications of the proposed rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act. The proposal would impose direct one-time costs associated with changing product labels, but that cost is estimated to total less than \$1 million.

Because the agency has not previously invited specific comment on the economic impact of a requirement of interim labeling of OTC drug products containing water-soluble gums as active ingredients, a period of 60 days from the date of publication of this proposed rulemaking in the *Federal Register* will be provided for comments on this subject to be developed and submitted. 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.

The agency has determined under 21 CFR 25.24(c)(6) 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.

Interested persons may, on or before December 31, 1990, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 31, 1990. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this

document, and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, it is proposed that subchapter C of chapter I of title 21 of the Code of Federal Regulations be amended in part 201 as follows:

PART 201—LABELING

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 508, 507, 508, 510, 512, 701, 704, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 357, 358, 380, 380b, 371, 374, 378); secs. 215, 301, 351, 354-380F, 381 of the Public Health Service Act (42 U.S.C. 216, 241, 282, 283b-283n, 284).

2. Section 201.319 is added to read as follows:

§ 201.319 Water-soluble gums, hydrophilic gums, and hydrophilic mucilloids (including but not limited to agar, alginic acid, carboxymethylcellulose sodium, carrageenan, chondrus, glucomannan ((B-1,4 linked) polymannose acetate), guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil, tragacanth, and xanthan gum); required warning.

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that esophageal obstruction and asphyxiation have been associated with the ingestion of water-soluble gums, hydrophilic gums, and hydrophilic mucilloids including but not limited to agar, alginic acid, carboxymethylcellulose sodium, carrageenan, chondrus, glucomannan ((B-1,4 linked) polymannose acetate), guar gum, karaya gum, kelp, methylcellulose, plantago seed (psyllium), polycarbophil, tragacanth, and xanthan gum. Esophageal obstruction and asphyxiation due to orally-administered drug products containing water-soluble gums, hydrophilic gums, and hydrophilic mucilloids as active ingredients are significant health risks when these products are taken without adequate

fluid or when they are used by individuals with esophageal narrowing or dysfunction, or with difficulty in swallowing.

(b) Any drug products containing water-soluble gums, hydrophilic gums, and hydrophilic mucilloids for human use in oral dosage forms are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following warning in bold print and capital letters:

Warning: (Select one of the following, as appropriate: TAKE or MIX) THIS PRODUCT WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID. TAKING THIS PRODUCT WITHOUT ADEQUATE FLUID MAY CAUSE IT TO SWELL AND BLOCK YOUR THROAT OR ESOPHAGUS AND MAY CAUSE CHOKING DO NOT TAKE THIS PRODUCT IF YOU HAVE EVER HAD DIFFICULTY IN SWALLOWING OR HAVE ANY THROAT PROBLEMS. IF YOU EXPERIENCE CHEST PAIN, VOMITING, OR DIFFICULTY IN SWALLOWING OR BREATHING AFTER TAKING THIS PRODUCT, SEEK IMMEDIATE MEDICAL ATTENTION.

Dated: September 1, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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