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, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule requiring specific warning and direction statements in the labeling of all over-the-counter (OTC) drug products containing as active ingredients water-soluble gums, hydrophilic gums, and hydrophilic mucilloids, including, but not limited to, agar, alginic acid, calcium polycarbophil, 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. The warning and direction statements will 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 final rule after evaluating reports of esophageal obstruction and asphyxiation involving OTC drug products containing water-soluble gums as active ingredients. Water-soluble gums as active ingredients have been used in OTC antidiarrheal, laxative, and weight control drug products. They are currently used primarily in OTC laxative drug products and are under review in the ongoing rulemaking for OTC laxative drug products as part of FDA's OTC drug review. FDA has determined that implementation of specific warning and direction statements for these ingredients should not await completion of the OTC drug review process. Therefore, the warning and direction statements will now be required to support the safe use of OTC drug products containing water-soluble gums as active ingredients. The warning and direction statements will be incorporated into the pertinent OTC drug monographs as the rulemakings for these drug products are completed.

EFFECTIVE DATE: February 28, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

SUPPLEMENTARY INFORMATION: In the Federal Register of October 30, 1990 (55 FR 45782), FDA proposed to amend 21 CFR part 201, subpart G, *Specific Labeling Requirements for Specific Drug Products*, to require a warning for all OTC drug products containing water-soluble gums as active ingredients. The agency proposed 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." The agency considered 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 have primarily been 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, alginic acid, calcium polycarbophil, carboxymethylcellulose sodium, carrageenan, glucomannan [1], guar gum, karaya gum, kelp [2], methylcellulose, plantago seed (psyllium) [3], polycarbophil, polycarbophil calcium, tragacanth, and xanthan gum. The ingredients polycarbophil and calcium polycarbophil 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 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.

As discussed in the proposed rule (55 FR 45782 at 45783 to 45784), 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 191 cases of esophageal obstruction and 8 cases of asphyxia associated with orally-administered OTC laxative and weight control products containing these ingredients between 1970 and May, 1992. Death occurred in 18 of these cases (Refs. 1 and 2).

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 the 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

[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, 1992."

[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, 1992."

compromise of the intestinal lumen, (40 FR 12908).

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 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. 3):

> 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.

In the **Federal Register** of November 7, 1990 (55 FR 46914), FDA published a final rule establishing that certain active ingredients in OTC drug products are not generally recognized as safe and effective or are misbranded. Among the ingredients listed in this final rule under active ingredients for bulk laxative drug products were agar, carrageenan (degraded), carrageenan (native), and guar gum. No substantive comments or new data had been submitted to support the reclassification of any of these ingredients to monograph status. The final rule stated that the listed active ingredients should be eliminated from OTC drug products by May 7, 1991, regardless of whether further testing was undertaken to justify future use, and regardless of whether the relevant OTC drug monographs had been finalized by that date. Therefore, on or after May 7, 1991, no OTC laxative drug product containing any of these four water-soluble gum active ingredients could be initially introduced or initially delivered for introduction into interstate commerce unless it was the subject of an approved application.

In its report on OTC weight control drug products, published in the **Federal Register** of February 26, 1982 (47 FR 8466), the Miscellaneous Internal Panel classified the water-soluble gums alginic acid, carboxymethylcellulose sodium, carrageenan, 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).

In the **Federal Register** of October 30, 1990 (55 FR 45788), the agency published a notice of proposed rulemaking stating that certain ingredients in OTC weight control drug products are not generally recognized as safe and effective and are misbranded. Among the ingredients proposed as nonmonograph were the water-soluble gums, alginic acid, carboxymethylcellulose sodium, carrageenan, chondrus, guar gum, karaya gum, kelp, methylcellulose, plantago seed, and xanthan gum. The agency determined that no substantive comments or additional data had been submitted to the OTC drug review to support any of these ingredients as being generally recognized as safe and effective in OTC weight control drug products.

In the **Federal Register** of March 6, 1991 (56 FR 9312), the agency issued a clarification of this October 30, 1990, notice of proposed rulemaking. The purpose of this clarification was to make clear that the addition of the proposed warning statement in product labeling was not a sufficient basis to permit the continued marketing of OTC weight control drug products containing guar gum.

In the **Federal Register** of August 8, 1991 (56 FR 37792), FDA issued a final rule establishing that certain active ingredients in OTC weight control drug products are not generally recognized as safe and effective or are misbranded. Among the ingredients subject to this final rulemaking are the water-soluble gums alginic acid, carboxymethylcellulose sodium, carrageenan, chondrus, guar gum, karaya gum, kelp, methylcellulose, plantago seed, and xanthan gum. On or after February 10, 1992, no OTC drug product containing any of these active ingredients for weight control use could be initially introduced or initially delivered for introduction into interstate commerce unless it was the subject of an approved application.

Although many drug products containing these water-soluble gums can no longer be initially introduced or initially delivered for introduction into interstate commerce, laxative drug products containing the water-soluble gums carboxymethylcellulose sodium, karaya gum, methylcellulose, polycarbophil, and psyllium may continue to be marketed. In addition, water-soluble gums may be present as active ingredients in other than laxative and weight control drug products, e.g., polycarbophil in antidiarrheal drug products. Accordingly, the agency is requiring these new warning and direction statements at this time, without waiting for the completion of any OTC drug review rulemakings related to such products.

In response to the proposed rule requiring a warning in the labeling of all OTC drug products containing water-soluble gums as active ingredients, nine manufacturers, one drug manufacturers' association, one individual, one health department, and six professional associations submitted comments. Copies of the comments received are on public display in the Dockets Management Branch, Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

[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 carrageenan.

References

(1) Department of Health and Human Services, FDA, Adverse Drug Reaction Reports for the years 1971 to 1992, in OTC

Volume 20 FR, Docket No. 90N–0200, Dockets Management Branch.

(2) Adverse Drug Reaction Reports, Reference No. 7 in OTC Volume 20 TFR, Docket No. 90N–0200, Dockets Management Branch.

(3) Comment No. C00100, Docket No. 78N–036L, Dockets Management Branch.

I. The Agency's Conclusions on The Comments

1. One comment supported the intent of the proposed warning for OTC drug products containing water-soluble gums, stating that there is sufficient evidence to mandate the inclusion of a warning for these products. Another comment stated that the warning requirement is appropriate and is preferable to FDA's October 30, 1990, proposal (55 FR 45788) to ban the use of guar gum in OTC weight control drug products. The comment added that the warning would allow consumers to continue using products they wish to use, while eliminating the potential for safety hazards in connection with such products.

The agency notes that this current rulemaking does not allow the use of guar gum in OTC weight control drug products even with the accompanying warning label. Since this comment was submitted, the agency published a clarification notice (March 6, 1991, 56 FR 9312) and a final rule for OTC weight control drug products (August 8, 1991, 56 FR 37792), in which it concluded that certain active ingredients, including guar gum, in OTC weight control drug products are not generally recognized as safe and effective and are misbranded. Accordingly, use of the warning and direction statements provided for in this final rule is not a basis for the continued use of guar gum or any other water-soluble gums as an active ingredient in OTC weight control drug products. As noted above, the warning and direction statements must appear on all OTC drug products containing a water-soluble gum as an active ingredient, including OTC bulk-forming laxative drug products containing carboxymethylcellulose sodium, karaya gum, methylcellulose, psyllium, or polycarbophil as an active ingredient.

2. Three comments stated that a warning is not necessary for water-soluble gum products because adverse reactions were reported by only a very small percentage of product users. Two comments suggested that the situation could be handled by manufacturers identifying the water-soluble gum ingredients on the product label so that the subpopulation of sensitive individuals can avoid these products. The comments stated that this approach is consistent with the FDA's long-term policy regarding the identification of ingredients as the primary means of notifying sensitive individuals who may react to certain ingredients. Two comments noted that even though many common foods (e.g., milk, eggs, nuts, shellfish) cause adverse reactions, which range from mild to life-threatening, in subgroups of the population, they are not required to have warning labels.

The agency agrees that listing ingredients on the product label is necessary and often sufficient to alert consumers who are sensitive to certain ingredients. In the present case, however, the problem presented is not one of the sensitivity of a subset of the population but of vulnerability to serious adverse outcomes in all members of the population who use the drugs incorrectly. The purpose of the warning for drug products containing water-soluble gums is to ensure that consumers know how to use the products safely, specifically, in a way that avoids esophageal obstruction. Merely identifying the water-soluble gum ingredient(s) on the product label would not alert consumers to the problem or to the remedy. Foods are discussed in comment 3.

3. One comment, which agreed with the need for a warning statement for OTC drug products containing water-soluble gums, recommended that the agency also address food products that contain approximately the same amount of these ingredients per serving as is used in a dose of certain OTC drug products. The comment mentioned a cereal product that contains 3.5 to 3.7 grams (g) of psyllium per serving, and an OTC laxative drug product containing 3.6 g of psyllium per dose. The comment was concerned that individuals taking both the OTC laxative drug product and one or more servings of such a cereal would increase their odds of having esophageal or bowel obstruction.

The agency is aware that there are many food products on the market containing water-soluble gums. The agency is concerned about the potential hazards of these ingredients, whether present in drug or food products, and has established standards for a number of water-soluble gums used as food additives. For example, the use of psyllium as an optional ingredient in certain frozen desserts at levels not exceeding 0.5 percent was provided for in a final rule establishing standards of identity for frozen desserts published by the agency in 1960 (25 FR 7126, July 27, 1960). Maximum usage levels also have been set for guar gum (21 CFR 184.1339), agar-agar (21 CFR 184.1115), karaya gum (21 CFR 184.1349), and gum tragacanth (21 CFR 184.1351). The percentage of water-soluble gums allowed in food products is generally low, and the agency has not seen any problems of esophageal obstruction or asphyxiation associated with the use of water-soluble gums at these levels in food products.

Although water-soluble gums used in food products are not included in this rulemaking, the agency will continue to evaluate and monitor these ingredients when they are used in any products marketed for human consumption. Appropriate warnings will be proposed if a need to do so is found to be necessary.

4. Several comments suggested that the proposed warning for OTC drug products containing water-soluble gums should apply only to products in a dry or unhydrated form. One comment mentioned that the cases of esophageal obstruction discussed in the proposed rule (55 FR 45782 at 45783) referred to gums in tablet form and agreed that the proposed warning is appropriate for this type of product. However, the comment contended that insufficient evidence exists to mandate the proposed warning for OTC drug products containing water-soluble gums in powder form which are dissolved in 8 oz of water prior to ingestion. The comment argued that little evidence exists that such water-based products, when taken according to the label directions by individuals without esophageal or throat problems, pose a risk of asphyxiation or esophageal obstruction.

The agency agrees that water-soluble, gum-containing products that are marketed in a fully hydrated form (e.g., in a solution) do not pose any significant risk of causing esophageal obstruction and that the warning statement is not necessary for those products. The problem with esophageal blockage associated with the use of water-soluble, gum-containing OTC drug products has been limited to those products marketed in the unhydrated form. Products that are marketed in a dry or incompletely hydrated state (intended to be dissolved in water by the consumer prior to ingesting, or taken with water or other liquid), whether in tablet (see comment 5), capsule, powder, or other form, have the potential for causing obstruction if the product is taken with inadequate fluid or if it is taken by individuals with swallowing or other throat problems. The agency acknowledges that the dosage forms involved in the cases of esophageal obstruction due to guar gum, which were discussed in the proposed

rule (55 FR 45782 at 45783), were tablets. However, a number of cases of esophageal obstruction due to other water-soluble gums have involved different dosage forms (e.g., powdered forms of psyllium, and granular forms of psyllium, karaya gum, and tragacanth) (see 55 FR 45783 and 45784: specifically references 7 through 10, 13, 15, and 16). Although dry forms of water-soluble gums could be hydrated according to label directions, prior to ingestion, and safely used by most consumers, the agency believes a warning will decrease the extent to which these products could be misused by some individuals with possible adverse consequences. Further, the agency does not have any data to show how much time is necessary to fully hydrate these products after mixing them with water. The agency therefore concludes that it is appropriate to require the warning for all dosage forms of OTC drug products containing water-soluble gums as active ingredients in dry or incompletely hydrated form, including those intended to be hydrated by the consumer (i.e., with label directions to dissolve the product in water). The agency has included this information in new § 201.319(b). Those OTC drug products marketed in a completely hydrated form will not require the warning.

5. One comment agreed that the proposed warning is appropriate for OTC drug products containing water-soluble gums in tablet form, but contended that the warning would be inaccurate for two-piece, hard-shell capsules that require significant exposure to fluid before dissolving. The comment claimed such an environment does not exist in the throat and therefore the risk is moot. The comment added that virtually all reports of esophageal blockage cited by the agency in the proposal (55 FR 45782 at 45783) involved tablets. The comment recommended that the warning be modified for water-soluble gums marketed in two-piece, hard-shell capsules to read as follows:

> Take this product with at least 8 ounces (a full glass) of water or other fluid. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention.

The comment concluded that this approach would encourage industry to adopt the safest known dosage forms and would minimize potential consumer confusion and loss of confidence in the safety of many other OTC drug products offered as capsules and tablets.

As discussed in comment 4, the agency is aware of numerous cases of esophageal obstruction due to various dosage forms of water-soluble gum OTC drug products (i.e., tablets, granules, powder). Although capsules may be a safer dosage form than tablets for administering water-soluble gums, the agency believes capsules could also be potentially hazardous if they are chewed or otherwise broken before or during ingestion. For instance, a consumer who has difficulty swallowing may chew the capsule to allow for greater ease in swallowing, thereby releasing the capsule contents in the throat or esophagus. Because of the small size of the released particles, greater hydration and greater swelling could occur from the broken capsule than from a tablet. Therefore, because esophageal obstruction could occur when capsules are broken, the agency believes that safer consumer use would result by having the same warnings for capsules as other dosage forms containing water-soluble gums. Accordingly, the warning in § 201.319(b) is being required for all dosage forms (e.g., capsules, granules, powders, tablets, wafers) of unhydrated water-soluble gums when used as active ingredients in OTC drug products. However, the agency will consider exempting a water-soluble gum product from the warning statements on the basis of data demonstrating that no swelling occurs for that particular ingredient in a specific dosage form or formulation. Such requests for exemption from the warning should be submitted in the form of a citizen petition as provided in § 10.30 (21 CFR 10.30). However, the mere submission of a citizen petition does not allow an exemption from the required warning while the citizen petition is being evaluated.

6. Four comments objected to the proposed warning statements being applicable to psyllium, calcium polycarbophil, and methylcellulose dry powder. Two comments contended that the proposed warnings should not apply to psyllium on the basis of a 1982 evaluation by the Select Committee of GRAS Substances (a group of leading food experts). This Committee reviewed 60 years of data on psyllium and stated (Ref. 1):

> There is no evidence in the available information on psyllium seed husk gum that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.

One comment stated that calcium polycarbophil is not a soluble fiber and does not swell appreciably in the upper gastrointestinal tract. The comment contended that, based on the drug's chemical characteristics and reported adverse drug reactions, esophageal obstruction due to swelling of the product is not an adverse reaction associated with calcium polycarbophil. Another comment contended that the proposed warnings are not appropriate for the methylcellulose dry powder formulation used in its product because there is no evidence that this formulation causes esophageal obstruction. The comment submitted results of some simple in-vitro comparison tests carried out by mixing methylcellulose-based formulations and ground psyllium-based formulations with grossly underrecommended quantities of water and observing the resulting properties of the mixtures. The comment argued that, even when dispersed in inadequate amounts of water, its methylcellulose formulation does not form a gel that could cause esophageal obstruction. The comment requested a hearing on this issue.

The comments' arguments that the proposed warnings should not apply to specific water-soluble gums are not persuasive. Because ingestion of water-soluble gums with inadequate amounts of fluid or by individuals with difficulty in swallowing could potentially cause esophageal obstruction, the agency believes that the warning statements are necessary to ensure the safe use of these drug products. Swelling and increased bulk are known results of adding water to a water-soluble gum. Even though different formulations and types of gums vary in their swelling volume, the degree of swelling remains uncertain. Although the in-vitro tests indicated a difference in the viscosities of methylcellulose-based formulations and ground psyllium-based products, no data were submitted to indicate how these results would apply to the in-vivo situation, where variables such as individual body temperature, additional food intake, or esophageal motility might affect the ingredients. The agency concludes that it cannot accept contentions of no evidence of a hazard as a basis for exempting specific water-soluble gum ingredients from the warning requirement. As noted in comment 5, the agency will consider an exemption from the required warning. The agency concludes that, without adequate data at this time, insufficient justification exists to grant a hearing.

Reference

(1) "Evaluation of the Health Aspects of Oat Gum, Okra Gum, Quince Seed Gum, and Psyllium Seed Husk Gum as Food Ingredients," Report of the Select Committee on GRAS Substances, Life Sciences Research

Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 1982.

7. Several comments contended that proposed § 201.319(b) is too broadly worded in that it requires the warning statement on any drug products containing water-soluble gums. The comments suggested that the warning be revised to clarify its application only to those drug products containing water-soluble gums as active ingredients. The comments stated that the warning was not necessary on drug products that contain water-soluble gums in small quantities as inactive ingredients because such products do not pose a risk of esophageal obstruction. Several comments mentioned that water-soluble gums are used as suspending agents in many liquid drug products for both prescription and OTC use, and claimed there is no risk of esophageal obstruction associated with those products. One comment added that certain water-soluble gums have been used as a tablet disintegrant for more than 25 years with no known adverse incidents.

The agency concurs that the warning should be clarified to state its application only to those OTC drug products containing water-soluble gums as active ingredients. Many currently marketed products contain water-soluble gums as inactive ingredients used as suspending agents, binders, tablet disintegrants, etc. The agency is not aware of any reports showing that the amount of a water-soluble gum used as an inactive ingredient produces the potential for esophageal obstruction and thus poses a threat to consumer safety. Accordingly, the agency is revising the language in the heading in § 201.319 to read: § 201.319 *Water-soluble gums, hydrophilic gums, and hydrophilic mucilloids (including * * *) as active ingredients; required warnings and directions*, and paragraph (b) of § 201.319 to read: "Any drug products for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient in an oral dosage form when marketed in a dry or incompletely hydrated form as described in paragraph (a) of this section are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following warnings and directions in bold print and capital letters: * * *."

8. Three comments contended that the concerns raised by the proposed warning statements for OTC drugs containing water-soluble gums could be adequately addressed under "Directions for Use." One comment mentioned that the first statement of the proposed warning currently exists under "Directions for Use" for OTC bulk-forming laxatives. Another comment stated that the directions for use found on its product label (both descriptive and pictorial) adequately convey appropriate product use, which is supported by actual consumer experience. The comment mentioned the very low incidence rate of serious esophageal blockage reports for its products, which are mixed with liquid prior to ingestion. The comment requested an oral hearing if the agency disagrees with its position and maintains that the warning is warranted (for its product).

Two comments suggested adding the following sentence to the "Directions for Use": "Taking this product without enough liquid may cause choking." One of the comments stated that the term "choking" encompasses several of the other proposed consequence terms of the warning and thus would eliminate the need for the part of the proposed warning that states: "If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention." The comment recommended that the proposed warning appear under the "Directions for Use" as follows:

(Select one of the following, as appropriate: "Take" or "Mix") "this product with at least8 ounces (a full glass) of liquid. Taking this product without enough liquid may cause choking."

Three comments suggested an alternative to the proposed warning in the form of an "instructive warning," which states: "*VERY IMPORTANT*—Take (or mix) this product with at least 8 ounces (a full glass) of water or other fluid."

The agency has considered the comments' recommendations and agrees that information conveying the proper use of OTC water-soluble, gum-containing drug products should be included under the "Directions" section of the product's labeling (see also comment 9). Therefore, the agency is establishing a "Directions" section in § 201.319 that states: "(Select one of the following as appropriate: 'TAKE' or 'MIX') 'THIS PRODUCT (CHILD OR ADULT DOSE) WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID. TAKING THIS PRODUCT WITHOUT ENOUGH LIQUID MAY CAUSE CHOKING. SEE WARNINGS." This new direction statement will be required in the labeling of OTC water-soluble, gum-containing drug products upon the effective date of this final rule. At a later date, when the final rules for OTC laxative and antidiarrheal drug products are published, the warnings and directions included under § 201.319 will be incorporated into the labeling of bulk laxative drug products in § 334.52 and antidiarrheal drug products in § 335.50, respectively.

The agency concludes that critical information alerting the consumer about the possible consequences of not taking these products correctly should be appropriately placed in both the "Warnings" and the "Directions" sections of the products' labeling. The agency believes that the significance of the information will be emphasized if it appears in both sections of the labeling. Further, because of possible adverse reactions that can occur if the product is not taken correctly, the agency considers it very important that consumers' attention also be directed to the warning information. Therefore, to help draw attention to the warning statement, the agency is also adding the phrase "SEE WARNINGS" at the end of the "Directions" in § 201.319, to read: "(Select one of the following as appropriate: 'TAKE' or 'MIX') 'THIS PRODUCT (CHILD OR ADULT DOSE) WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID. TAKING THIS PRODUCT WITHOUT ENOUGH LIQUID MAY CAUSE CHOKING. SEE WARNINGS."

The agency denies one comment's request for a hearing at this time because of a lack of adequate data showing that the warning is not warranted for a specific product. However, as noted in comment 5, the agency will consider requests for an exemption from the warning, submitted in the form of a citizen petition as provided in § 10.30. Interested parties must provide documentation of the safety and low incidence rate of esophageal blockage for their specific product(s) in the citizen petition.

9. One comment contended that the proposed warning is inaccurate, overly broad in scope, and would not serve properly to warn consumers. The comment pointed out that the requirement to state "at least 8 ounces (a full glass) of water or other fluid" does not take into account the lower recommended dosages for some of these ingredients for children ages 6 to under 12. The comment stated that lesser amounts of liquid are appropriate for those users, and the warning should be modified to recognize the different dosages for these products.

The purpose of the warning is to ensure safe and effective use by both adults and children of OTC drug products containing water-soluble gums

as active ingredients; specifically, to prevent esophageal blockage that could result from taking or mixing these drugs with inadequate amounts of water or from use by individuals with swallowing difficulties. Although the maximum single dose of water-soluble gums for children (ages 6 to under 12) generally equals one-half the maximum single dose for adults, the minimum single dose for children is frequently the same as that for adults. For instance, in the tentative final monograph for OTC laxative drug products, the agency proposed that the minimum single dose of psyllium as a bulk forming laxative for both adults and children (ages 6 to under 12) is 2.5 g (51 FR 35136 at 35137). Similarly, for methylcellulose and sodium carboxymethylcellulose the proposed minimum single dose for adults and children is 0.45 g. Thus, because a child (age 6 to under 12) would take the same minimum single dose as an adult, the child would need to consume the same amount of fluid to avoid swelling and possible blockage problems. Therefore, the directions statement included in this final rule state that the same amount of fluid (at least 8 oz) should be taken with both children's and adult's doses of water-soluble gum products.

10. A number of comments suggested revising the third and fourth sentences of the proposed warning, which state:

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 comments described these statements as "unduly alarming," "without sufficient justification," "not easily understood," "too strongly worded," "too broad and too vague," and "ambiguous." Several of the comments contended that the phrase "if you have ever had difficulty in swallowing or have any throat problems" could apply to almost all consumers because nearly everyone at some time has had a sore throat (from a cold, cough, minor irritation, or smoking) that resulted in difficulty in swallowing. Several comments expressed concern that if people take the warning literally, the market for water-soluble, gum-containing OTC drug products would be severely damaged. The comments mentioned that many of the water-soluble gums are already generally recognized as safe as food ingredients, and that these products are currently being used safely by millions of people.

Two comments argued that the statement about difficulty in swallowing or throat problems should be eliminated or, if retained, modified to refer only to persons with diagnosed swallowing problems or a history of throat problems. Another comment suggested modifying the statement to read: "Do not take this product if you have esophageal narrowing or dysfunction."

Two comments suggested revising the proposed warning statement to direct individuals with throat problems to seek the advice of a doctor prior to using the product. One comment suggested the following: "If you have been diagnosed with a condition that causes difficulty in swallowing, consult a doctor before using this product." The other comment suggested different wording, as follows: "If you have been diagnosed with esophageal narrowing or have difficulty swallowing, consult a doctor before taking this product."

The agency agrees that the third sentence of the proposed warning could be revised to make the statement more specific. Individuals who have had swallowing difficulties in the past due to minor sore throat, colds, or coughs need not be excluded from taking water-soluble gum drug products; however, individuals with medically-related swallowing problems must be warned to avoid these products. The agency does not believe a statement advising consumers with swallowing difficulties to seek the advice of a doctor before taking this type of product is appropriate because water-soluble, gum-containing products should not be taken by those individuals. Further, the agency does not believe that the terms "esophageal narrowing" or "esophageal dysfunction" should be used in the warning because they are too technical. The agency believes that the term "difficulty in swallowing" is better understood by consumers. The agency also is not including the term "diagnosed" in the warning statement because individuals could have throat problems without the problems having been diagnosed by a physician. None of the comments requested a specific revision in the fourth sentence of the warning. If chest pain, vomiting, or difficulty in swallowing occur after taking a water-soluble gum-containing drug product the agency finds it appropriate to alert consumers to seek immediate medical attention. Accordingly, in this final rule, the third sentence of the warning statement is revised and the fourth sentence remains as proposed, to read:

DO NOT TAKE THIS PRODUCT IF YOU HAVE DIFFICULTY IN SWALLOWING. IF YOU EXPERIENCE CHEST PAIN, VOMITING, OR DIFFICULTY IN SWALLOWING OR BREATHING AFTER TAKING THIS PRODUCT, SEEK IMMEDIATE MEDICAL ATTENTION.

11. One comment stated that if this final rule becomes effective before the monographs for OTC laxative and weight control drug products, it must provide adequate time for manufacturers to develop and implement new labeling. The comment recommended that the effective date of any final rule be at least 12 months after the date of publication in the Federal Register, and that consideration be given to requests for limited extensions based on extenuating circumstances.

A final rule on OTC weight control drug products containing water-soluble gum active ingredients was published in the Federal Register of August 8, 1991 (56 FR 37792). All water-soluble gum active ingredients were found to be not generally recognized as safe and effective for this use. A final rule for OTC laxative and for OTC antidiarrheal drug products will not be published until after this final rule for water-soluble gums becomes effective. The final rules for OTC laxative and antidiarrheal drug products may include several water-soluble gum active ingredients. Drug products containing these active ingredients will need to be relabeled to bear the directions and warning statements required by this final rule (21 CFR 201.319) before the final monographs for OTC laxative and antidiarrheal drug products become effective. Normally, when a monograph is published, the agency provides a 12-month period for any necessary reformulation, relabeling, and stability testing that needs to be done. In the current situation, no reformulation or stability testing needs to be done. The only required action is relabeling to add several additional statements. The agency recognizes that in order for manufacturers to comply with this final rule for OTC drug products containing water-soluble gums, new labels will have to be written, ordered, received, and incorporated into the manufacturing process. However, this required relabeling relates to a safety problem, for which the agency has determined that a shorter deadline than the customary 12 months should be established. Therefore, this final rule will be effective 6 months after the date of publication in the Federal Register. The agency believes that 6 months is sufficient time for most manufacturers to bring their products into compliance with this final rule, which affects only the labeling of the product. Therefore, any OTC drug product that is subject to

this rule that is initially introduced or initially delivered for introduction into interstate commerce, or that is repackaged or relabeled, after the effective date of the rule must be in compliance with the rule regardless of the date the product was manufactured, initially introduced, or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with this rule at the earliest possible date. Requests for a limited extension of time will be considered by the agency only if extenuating circumstances are adequately documented. Any such requests should be sent to the Food and Drug Administration, Division of Drug Labeling Compliance (HFD–310), 7520 Standish Pl., Rockville, MD 20855.

II. Summary of Significant Changes From The Proposed Rule

1. The agency has clarified § 201.319 to state that the warning and direction statements apply only to OTC drug products containing a water–soluble gum as an active ingredient. (See comment 7.)

2. The agency has revised § 201.319(b) to indicate that the warning and direction statements are required only for water-soluble gum products marketed in a dry or incompletely hydrated form. (See comments 4 and 5.)

3. The agency is deleting the first sentence of the warning proposed in § 201.319(b) and is, instead, adding "Directions" in § 201.319(b) that state: (Select one of the following, as appropriate: "TAKE" or "MIX") "THIS PRODUCT (CHILD OR ADULT DOSE) WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID. TAKING THIS PRODUCT WITHOUT ENOUGH LIQUID MAY CAUSE CHOKING. SEE WARNINGS." (See comment 8.) These directions indicate that the same amount of fluid (at least 8 ounces) should be mixed or taken with the product by an adult as well as a child. (See comment 9.)

4. The agency is revising the third sentence of the warning statement proposed in § 201.319 to read: "DO NOT TAKE THIS PRODUCT IF YOU HAVE DIFFICULTY IN SWALLOWING." (See comment 10.)

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

Based on available evidence, the agency is issuing a final rule requiring specific warning and direction statements in the labeling of all OTC drug products for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient when marketed in a dry or incompletely hydrated form to include, but not limited to, the following dosage forms: capsules, granules, powders, tablets, and wafers. 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 swallowing. Therefore, the agency is requiring specific warning and direction statements for all OTC drug products containing water-soluble gums as active ingredients prior to the completion of rulemakings for certain classes of OTC drug products that contain these ingredients. These ingredients include, but are not limited to, agar, alginic acid, calcium polycarbophil, 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. (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 this final regulation.)

Because of the potential serious health risk involved, the warning and direction statements must appear in bold print and in capital letters. The required statements are as follows:

"*WARNINGS*: 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 DIFFICULTY IN SWALLOWING. IF YOU EXPERIENCE CHEST PAIN, VOMITING, OR DIFFICULTY IN SWALLOWING OR BREATHING AFTER TAKING THIS PRODUCT, SEEK IMMEDIATE MEDICAL ATTENTION."

DIRECTIONS: (Select one of the following, as appropriate: "TAKE" or "MIX") "THIS PRODUCT (CHILD OR ADULT DOSE) WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID. TAKING THIS PRODUCT WITHOUT ENOUGH LIQUID MAY CAUSE CHOKING. SEE WARNINGS."

The warning and direction statements in § 201.319 will be incorporated into the labeling contained in the monographs for OTC laxative and antidiarrheal drug products, or any other applicable monograph, as the monographs are finalized. The agency concludes that it would be an unacceptable health risk to delay implementation of these warning and direction statements until these rulemakings are completed. Manufacturers are encouraged to comply with this final rule at the earliest possible date.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (55 FR 45782 at 45784). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for specific warning and direction statements for OTC drug products containing water-soluble gums as active ingredients, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC drugs containing water-soluble gums as active ingredients is not expected to pose such an impact on small businesses. The final rule will impose direct one- time costs associated with changing product labels, but that cost is estimated to total less than $1 million. Manufacturers will have 6 months in which to implement this relabeling. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.319 is added to subpart G to read as follows:

§ 201.319 Water-soluble gums, hydrophilic gums, and hydrophilic mucilloids (including, but not limited to agar, alginic acid, calcium polycarbophil, 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) as active ingredients; required warnings and directions.

(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, calcium polycarbophil, 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 hydrophylic 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. Additional labeling is needed for the safe and effective use of any OTC drug product for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient when marketed in a dry or incompletely hydrated form to include, but not limited to, the following dosage forms: capsules, granules, powders, tablets, and wafers.

(b) Any drug products for human use containing a water-soluble gum, hydrophilic gum, or hydrophilic mucilloid as an active ingredient in an oral dosage form when marketed in a dry or incompletely hydrated form as described in paragraph (a) of this section are misbranded within the meaning of section 502 of the Federal Food, Drug, and Cosmetic Act unless their labeling bears the following warnings and directions in bold print and capital letters:

"*WARNINGS*: 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 DIFFICULTY IN SWALLOWING. IF YOU EXPERIENCE CHEST PAIN, VOMITING, OR DIFFICULTY IN SWALLOWING OR BREATHING AFTER TAKING THIS PRODUCT, SEEK IMMEDIATE MEDICAL ATTENTION."

"*DIRECTIONS*:" (Select one of the following, as appropriate: "TAKE" or "MIX") "THIS PRODUCT (CHILD OR ADULT DOSE) WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID. TAKING THIS PRODUCT WITHOUT ENOUGH LIQUID MAY CAUSE CHOKING. SEE WARNINGS."

(c) After February 28, 1994, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce, or any such drug product that is repackaged or relabeled after this date regardless of the date the product was manufactured, initially introduced, or initially delivered for introduction into interstate commerce, that is not in compliance with this section is subject to regulatory action.

Dated: August 19, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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