

proposed the direction "Drink a full glass (8 oz) of liquid with each dose" to define adequate fluid intake.

In the **Federal Register** of October 1, 1986 (51 FR 35136), FDA amended the TFM and proposed that bulk laxative ingredients be administered in divided doses rather than a single daily dose. The amendment was based on data that indicated the maximum daily dose of some bulk laxatives was so large that it may pose a risk of esophageal obstruction if taken at one time (51 FR 35136).

After receiving reports of cases of esophageal obstruction due to ingestion of laxative products containing water-soluble gums, hydrophilic gums, and hydrophilic mucilloids, including psyllium, FDA published a proposed rule in the **Federal Register** of October 30, 1990 (55 FR 45782), to require a warning in the labeling of all OTC drug products containing water-soluble gums as active ingredients. FDA added the warning to alert users to take adequate fluid and to avoid using these products if the person had previously experienced any difficulty in swallowing. FDA published a final rule requiring new warning and direction statements in the **Federal Register** of August 26, 1993 (58 FR 45194) and amended that rule in the **Federal Register** of March 17, 1999 (64 FR 13254 at 13292). The current warnings and directions (in § 201.319(b) (21 CFR 201.319(b)) state:

"Choking" [highlighted in bold type]: 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;" and

"Directions" [highlighted in bold type]: (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 choking warning."

II. Adverse Events Regarding Psyllium Ingredients in a Granular Dosage Form

A granular dosage form of psyllium, as a single ingredient product or a combination product containing psyllium (82 percent) and senna (18 percent), was introduced into the OTC market around 1979. In 1989, a major manufacturer of psyllium granular dosage form products reported to FDA 61 cases of esophageal obstruction and choking that occurred between February 1980 and December 1988 (Ref. 1). No deaths occurred, but these reports indicated that 19 people were

hospitalized and 31 people required medical intervention in the form of endoscopy to dislodge the esophageal obstructions. The same manufacturer had submitted a comment in 1985 (Ref. 2) to the laxative TFM stating that consumer labeling of psyllium containing laxatives should: (1) State that bulk-forming laxatives have the potential to block the esophagus, particularly in the presence of esophageal narrowing or when consumed with insufficient liquid, (2) bear a warning to drink sufficient amounts of fluid, (3) advise people with esophageal narrowing against using the product, and (4) direct individuals who experience esophageal obstruction, regurgitation, and difficulty swallowing to seek immediate medical attention. In response to the comment (Ref. 3), FDA suggested that the cases of esophageal blockage may be related to the manufacturer's directions for use, which instruct consumers to place the granules in the mouth and swallow, without chewing, prior to drinking liquid. FDA noted that other psyllium-containing OTC laxative drug products are mixed into liquid or food or, in the case of wafers and chewable tablets, chewed before swallowing. FDA indicated that it did not consider the manufacturer's directions for its products adequate to provide for their "safe OTC use" and suggested that, to retain OTC status, the manufacturer should consider reformulating the products to be suspended in "no less than 8 ounces of liquid per dose prior to consumption" or provide more specific labeling information indicating that the product is "not to be taken directly by spoon or swallowed dry." FDA stated that the manufacturer's products might require a new drug application (NDA) for use under medical supervision. FDA mentioned other reports of esophageal obstruction and asphyxiation associated with the ingestion of water-soluble gums, hydrophilic gums, and hydrophilic mucilloids, including psyllium.

In response to FDA's concerns (Ref. 4), the manufacturer noted that it took the following actions to resolve the problems of esophageal obstruction and choking: (1) In 1985, the directions for use were modified to emphasize the need to have adequate fluid intake, (2) a patient package insert was placed inside each package stressing the importance of taking sufficient liquid, and (3) a "dear doctor" letter was issued in February 1985 to U.S. physicians calling attention to the need for adequate fluid intake to avoid the risk of esophageal obstruction. The

manufacturer stated that only 15 of the 61 cases occurred after it took these actions.

As noted previously, on August 26, 1993, FDA published a final rule in the **Federal Register** requiring warning and direction statements in the labeling of all OTC drug products containing water-soluble gums as active ingredients, including psyllium. Additional warnings and directions were added to alert users to consume adequate fluid and to avoid using such products if the person had previously experienced any difficulty in swallowing.

Despite the new required warnings and directions and other labeling changes initiated by the manufacturer, FDA continued to receive reports of choking and esophageal obstruction associated with psyllium, particularly the granular dosage form. In November 2000, FDA reviewed reports (postmarketing safety review) from its adverse event reporting system (AERS) database and the medical literature for the time between 1966 and 2000 (Ref. 5). FDA identified 98 reported cases of esophageal obstruction and choking associated with the use of psyllium products (Ref. 6). Four deaths occurred and 66 cases required medical intervention and/or hospitalization. Of these 98 cases, 78 (80 percent), including 1 death and 59 cases that required medical intervention and/or hospitalization, were related to the granular dosage form that is swallowed unchewed while drinking liquid. Medical intervention included endoscopy (in 41 cases), esophageal dilatation, surgery, nasogastric tube, Heimlich maneuver, and polypectomy snare. The mean age in these cases (27 cases not reporting age) was 69 years. Possible risk factors were identified in 52 percent of the cases, although there were 37 cases with no reported or apparent risk factors.

FDA also identified 13 (11 percent) cases of choking-related events (and two cases of esophageal obstruction (2 percent)) related to a powder or wafer psyllium product. The label of these products stated that the powder should be mixed with 8 oz of liquid and the wafers should be consumed with 8 oz of liquid. The mean age in these cases was 71 years. There were three deaths (two from asphyxiation and one from bronchus obstruction) and seven people who required hospitalization. Three cases (4 percent) of choking and/or difficulty swallowing and four cases (5 percent) of esophageal obstruction were related to the use of another psyllium product available as a powder or toasted granules. The product directions indicated to mix the powder with liquid