

and sprinkle the granules on food. All seven cases (mean age was 64 years) required hospitalization.

Although these reports indicate there were fewer deaths related to the granular dosage form that was swallowed unchewed while drinking liquid (one out of four), there were significantly more overall cases of esophageal obstruction (78 out of 98) and cases that required medical intervention (59 out of 66) with this dosage form.

In January 2001, FDA requested and obtained updated adverse event reports from a current major manufacturer of psyllium laxative products in granular dosage form for the time period between January 1999 and January 2001 (Ref. 7). In April 2002, FDA received an update from this manufacturer for the time period after January 2001 (Ref. 8). This manufacturer's product labeling contained the following directions:

(1) Moisten your mouth with a drink of water or any cool beverage, (2) Place a teaspoonful of granules on your tongue. If you prefer, take only a partial teaspoonful at a time, (3) Without chewing, wash granules down with water or any cool beverage, (4) Repeat steps 1–3 until the recommended dose has been swallowed. Be sure to drink at least 8 ounces of cool liquid.

FDA's reviews (Refs. 9 and 10) of these reports identified 44 additional cases of adverse events related to esophageal obstruction between January 1999 and May 2002. No deaths were reported, but 13 of the reported cases were considered serious events requiring medical intervention (11 underwent endoscopy). The adverse event reports suggested that most of the people using the products followed the directions on the label (information on the dose taken was available in 36 out of 44 cases). Most people (27 out of 35) took sufficient fluid with the product, while insufficient fluid intake may have contributed to the esophageal obstruction in 7 cases.

In summary, FDA has received 142 cases of adverse events regarding esophageal obstruction and choking associated with psyllium between 1966 and May 2002. Of these 142 cases, 59 occurred after publication of the 1993 required warning (58 FR 45194) with 45 reported to have occurred during the last 3 years alone. Eleven of these 45 reported cases (25 percent) involved hospitalization and/or the need for invasive procedures.

Based on the data reviewed, and despite the warnings it has mandated, FDA now believes that there still exists a significant safety problem with esophageal obstruction associated with psyllium laxative products in granular dosage form, particularly products that

are swallowed dry, swallowed partially moistened prior to drinking liquid, and swallowed unchewed while drinking liquid. FDA is concerned that a consumer ingesting this granular dosage form is less likely to drink adequate amounts of fluid with the product than a consumer instructed to mix the product in 8 oz of fluid prior to ingestion. Multiple labeling changes, including additional warnings and enhanced directions to take adequate fluid, have not alleviated this problem. Rather, the problem seems to have worsened. During the first 10 years of marketing, 61 cases of esophageal obstruction were reported compared to 44 cases during the last 3 years alone. In addition, FDA is concerned that the incidence of serious adverse events for these products is underreported because reporting for products marketed under an OTC drug monograph is not currently mandatory.

III. FDA's Tentative Conclusion on OTC Psyllium Ingredients in a Granular Dosage Form

FDA now considers OTC laxative drug products containing psyllium ingredients in granular dosage form as presenting an unacceptable health risk to consumers. These drug products include, but are not limited to: (1) Any granules that are swallowed dry prior to drinking liquid, (2) any granules that are dispersed, suspended, or partially dissolved in liquid prior to swallowing, (3) any granules that are chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid, and (4) any granules that are sprinkled over food.

FDA continues to receive reports of esophageal obstruction and choking associated with these products despite the warning and direction statements required for all water soluble gums in § 201.319. Therefore, due to the significant safety risk these products pose, FDA is proposing to reclassify bulk laxative psyllium ingredients in granular dosage form from Category I (monograph) to Category II (nonmonograph). FDA proposes to add these ingredients in granular dosage form to the list of bulk laxatives in § 310.545(a)(12)(i) (21 CFR 310.545(a)(12)(i)) and to amend proposed § 334.10 (bulk-forming laxative active ingredients) to exclude the granular dosage form.

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not find so. Nor does FDA's requirement of warnings repudiate the prior OTC

drug regulations and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act (the act). This judgment balances the benefits of these drug products against their potential risks (see § 330.10(a) 21 CFR 330.10(a)). In the current situation, FDA has determined that warnings are not adequate to address the significant safety risks that these products pose.

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see "Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, final rule" (67 FR 72555, December 6, 2002).

Accordingly, if a final rule based on this proposal issues any drug product containing any psyllium ingredients in granular dosage form will be considered nonmonograph and misbranded under section 502 of the act (21 U.S.C. 352). This type of drug product would also be considered a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355), and set forth in part 314 of the regulations, is required for marketing. If a final rule is based on this proposal issues, it would apply to any OTC drug product containing psyllium ingredients in granular dosage form that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule. Further, any OTC drug product that was previously initially introduced or initially delivered for introduction into interstate commerce could not then be repackaged or relabeled after the effective date of the final rule.

IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–12), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and