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Assistant Chief Counsel for Regulations.

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SOCIAL SECURITY ADMINISTRATION

20 CFR Part 402

[Regulation No. 2; Docket No. SSA-2007-0020]

RIN 0960-AG46

Technical Amendments To Correct Cross-References

AGENCY: Social Security Administration.

ACTION: Correcting amendments.

SUMMARY: This document contains three technical corrections to our regulations. We are changing three cross-references because they are currently incorrect.

EFFECTIVE DATE: Effective on March 29, 2007.

FOR FURTHER INFORMATION CONTACT:

Rosemarie A. Greenwald, Social Insurance Specialist, Office of Regulations, Social Security Administration, 6401 Security Boulevard, Baltimore, MD 21235-6401. Call (410) 966-7813 or TTY 1-800-325-0778 for information about these correcting amendments. For information on eligibility or filing for benefits, call our national toll-free numbers 1-(800)-772-1213 or TTY 1-(800)-325-0778. You may also contact Social Security online at <http://www.socialsecurity.gov/>.

SUPPLEMENTARY INFORMATION: We are making corrections to our current regulations at 20 CFR 402.35(b)(2) which contain errors. The three cross-references in the last sentence of § 402.35(b)(2) incorrectly show §§ 404.984(b), 410.610c(b) and 416.1484(b). We are changing these to reflect the correct cross-references.

(Catalog of Federal Domestic Assistance Programs Nos. 96.001 Social Security—Disability Insurance; 96.002 Social Security—Retirement Insurance; 96.004 Social Security—Survivors Insurance and 96.006 Supplemental Security Income.

List of Subjects in 20 CFR Part 402

Administrative practice and procedure; Freedom of information.

Dated: March 21, 2007.

Paul Kryglik,

Acting SSA Regulations Officer.

■ For the reasons set out in the preamble, part 402 of chapter III of title 20 of the Code of Federal Regulations is

corrected by making the following correcting amendments:

PART 402—AVAILABILITY OF INFORMATION AND RECORDS TO THE PUBLIC

■ 1. The authority citation for part 402 continues to read as follows:

Authority: Secs. 205, 702(a)(5), and 1106 of the Social Security Act; (42 U.S.C. 405, 902(a)(5), and 1306); 5 U.S.C. 552 and 552a; 8 U.S.C. 1360; 18 U.S.C. 1905; 26 U.S.C. 6103; 30 U.S.C. 923(b); 31 U.S.C. 9701; E.O. 12600, 52 FR 23781, 3 CFR, 1987 Comp., p. 235.

■ 2. Section 402.35 is corrected by revising the last sentence of paragraph (b)(2) to read as follows:

§ 402.35 Publication.

* * * * *

(b) * * *

(2) * * * For a description of Social Security Acquiescence Rulings, see 20 CFR 404.985(c), 410.670c(b), and 416.1485(c) of this title.

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[FR Doc. E7-5494 Filed 3-28-07; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201 and 310

[Docket No. 1978N-0036L] (formerly Docket No. 1978N-036L)

RIN 0910-AF38

Laxative Drug Products for Over-the-Counter Human Use; Psyllium Ingredients in Granular Dosage Forms

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that over-the-counter (OTC) laxative drug products in granular dosage form containing the bulk-forming psyllium ingredients (psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), psyllium seed husks, plantago ovata husks, and plantago seed) are not generally recognized as safe and effective (GRASE) and are misbranded. This final rule includes, but is not limited to, any granules that are swallowed dry prior to drinking liquid; dispersed, suspended, or partially dissolved in liquid prior to swallowing; chewed, partially chewed,

or unchewed, and then washed down (or swallowed) with liquid; or sprinkled over food. FDA is issuing this final rule after considering reports of esophageal obstruction associated with the use of psyllium laxatives in granular dosage form. These cases continue to occur despite efforts to promote safe use through label warnings and directions. This final rule does not apply to psyllium laxatives in nongranular dosage forms, such as powders, tablets, or wafers. This final rule is part of FDA's ongoing review of OTC drug products.

DATES: *Effective Date:* This rule is effective October 1, 2007.

Compliance Date: The compliance date for all products subject to this final rule, including products with annual sales less than \$25,000, is October 1, 2007.

ADDRESSES: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts, and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Reynold Tan, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, MS 5411, Silver Spring, MD 20993-0002, 301-796-2090.

SUPPLEMENTARY INFORMATION:

I. Background

In the advance notice of proposed rulemaking (ANPRM) for OTC laxative, antidiarrheal, emetic, and antiemetic drug products (40 FR 12902 at 12906, March 21, 1975), the advisory review panel on OTC laxative, antidiarrheal, emetic, and antiemetic drug products (the Panel) recommended Category I (GRASE and not misbranded) status for the OTC bulk laxative psyllium ingredients, which included plantago seed, plantago ovata husks, psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), and psyllium seed husks. FDA concurred with the Panel's Category I classification of these ingredients in the tentative final monograph (TFM) published in the **Federal Register** of January 15, 1985 (50 FR 2124 at 2152).

In the ANPRM, the Panel recommended a warning statement (21 CFR 334.52(a)(1)) for bulk-forming laxatives that advised drinking a full glass, 8 ounces (oz), of liquid with each

dose and direction statements (§ 334.10(f)) advising adequate fluid intake (40 FR 12902 at 12942). The Panel concluded that adequate fluid intake was necessary for the proper use of bulk-forming laxatives, because esophageal and intestinal obstruction had occurred from ingesting bulk-forming laxatives with insufficient water or in the presence of certain disease conditions (40 FR 12908). FDA discussed in comments 36 and 37 of the TFM (50 FR 2124 at 2131 and 2132) 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. FDA 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 daily doses of bulk-forming laxative ingredients be administered in divided doses, rather than a single dose. The amendment was based on data that indicated the maximum daily dose of some bulk-forming laxatives was so large that it could pose a risk of esophageal obstruction if taken at one time (51 FR 35136).

Subsequently, cases of esophageal obstruction due to ingestion of laxative products containing water-soluble gums, hydrophilic gums, and hydrophilic mucilloids, including psyllium, were reported and 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 followed up by publishing 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."

FDA later considered data and other information about the safety of laxative products in granular dosage form containing psyllium, one of the active ingredients included in the water-soluble gum category. FDA tentatively concluded that these products posed an unacceptable safety risk, because esophageal obstructions continued to occur with these products despite requiring label warnings and directions. In the **Federal Register** of August 5, 2003 (68 FR 46133), FDA proposed an amendment to the laxative TFM to reclassify psyllium laxatives in granular dosage form from Category I to Category II (not GRASE or misbranded). In response to the proposed amendment, one manufacturer of a psyllium laxative product in a granular dosage form submitted a comment that is discussed in section II of this document.

II. FDA's Conclusions on the Comment

(Comment 1) The comment disagreed with FDA's proposal to reclassify psyllium laxative products in granular dosage form from Category I to Category II. The comment argued that the proposed rule should be withdrawn for the following reasons:

- FDA's analysis overstated the risks of granular psyllium. The comment stated that the number of events potentially related to psyllium products in granular dosage form is small relative to the number of doses taken by consumers. Further, of the 78 total cases of esophageal obstruction recorded for the company's granular dosage form product in FDA's Adverse Event Reporting System by the year 2000 (Ref. 1), only 17 cases had occurred since 1989. The comment's product was introduced to the U.S. market in 1980. Therefore, the comment contended that the 17 cases that occurred from 1989 to 2000 was not a basis for increased safety concern considering that 61 cases occurred from 1980 to 1989.

- FDA's analysis concentrated improperly on the granular dosage form of psyllium products.

The comment argued that the data reviewed by FDA contained information suggesting that psyllium products in powder dosage forms may present more serious safety problems (e.g., asphyxiation) than granular dosage forms. The comment further contended that because FDA published the August

26, 1993, final rule requiring warning and direction statements for all water-soluble gum products, FDA has focused solely on psyllium products in granular dosage form and ignored serious adverse effects associated with other dosage forms. The comment argued that the failure to use the same methods to obtain adverse events data for psyllium products in both granular and nongranular dosage forms undermines FDA's conclusion that only granular dosage forms pose an unacceptable risk. Of the 98 adverse events associated with all psyllium products recorded by FDA between 1966 to 2000 (Ref. 1), 3 deaths were associated with powder dosage forms compared to only 1 death associated with granular dosage forms, which the comment contended was not directly caused by the granular dosage form (Ref. 2). The comment stated that FDA emphasized the single fatality associated with psyllium laxatives in the granular dosage form, but ignored the fatalities associated with psyllium laxatives in nongranular dosage forms. The comment stated that the record of fatalities did not support FDA's conclusions concerning the risk from granular dosage forms containing psyllium. Rather, FDA should have requested safety records from manufacturers of nongranular dosage forms, similar to those requested from the distributor of a granular product.

- FDA failed to consider the benefits of granular psyllium products.

The comment contended that psyllium laxatives in granular dosage form are preferred by millions of consumers over powder and other forms, are the most widely used laxative drugs in the world, and have provided safe and effective relief for many years. The comment submitted an article (Ref. 3) that reported a clinical study comparing psyllium-containing products in granular and powder dosage forms in constipated subjects. In the study, the psyllium plus senna combination product in granular dosage form was significantly superior to the psyllium-only product in powder dosage form with respect to stool frequency, moisture content, and weight.

- FDA should consider foreign safety data.

The comment submitted listings of suspected foreign cases of dysphagia (difficulty in swallowing) associated with the use of its two psyllium laxative products in granular dosage form from 1980 to 2003 (Refs. 4 and 5). The comment reported three serious, and five nonserious, cases for the company's psyllium plus senna laxative in granular dosage form and six serious, and two

nonserious, cases for the company's psyllium-only laxative in granular dosage form. None of these cases resulted in serious injury or death.

(Response) FDA disagrees that its analysis overstated the risks of psyllium products in granular dosage form. While the number of adverse events reports of esophageal blockage associated with psyllium laxatives in granular dosage form is low relative to the number of doses taken, many of the reports describe serious medical consequences. Of the 78 reports of esophageal obstruction and choking-related events associated with psyllium laxatives in granular dosage form, 59 required hospitalization or medical intervention, including endoscopic procedures to remove blockages (68 FR 46133 at 46134). The manufacturer's claim that 1 death among 78 adverse events indicates the relative safety of the company's granular dosage form product ignores the fact that these 78 events represent most of the 98 total events of esophageal obstruction associated with all dosage forms containing psyllium reported between 1966 and 2000 (68 FR 46133 at 46134).

Although the comment claims that 17 case reports of esophageal obstruction from 1989 to 2000 should not be considered a basis for increased safety concern, FDA believes that reports of 44 adverse events related to esophageal obstruction reported between January 1999 and May 2002 (68 FR 46133 at 46135) does provide this basis. In 1993, FDA required labeling for all products containing water-soluble gums, including psyllium, to include a warning of possible esophageal obstruction and directions to take adequate fluid. Many of these recent events occurred even though the users had complied with the label directions. Thus, FDA has concerns that the problem of esophageal obstruction cannot be addressed through labeling. In addition, these adverse events are probably significantly underreported. OTC drugs without approved applications were not subject to mandatory reporting requirements, prior to the enactment of the Dietary Supplement and Nonprescription Drug Consumer Protection Act (S. 3546), which was signed by the President on December 22, 2006, and voluntary submission of reports by health professionals normally account for only about 10 percent of all reports in FDA's spontaneous reporting system. Under S. 3546, which amends the Federal Food, Drug, and Cosmetic Act, manufacturers, packers, or distributors of certain nonprescription drugs must report serious adverse events to FDA.

FDA acknowledges the occurrence of esophageal obstruction and choking-related events associated with psyllium laxatives in nongranular dosage forms. In 2000, FDA reviewed reports from its adverse event reporting system (AERS) database and the medical literature for esophageal obstruction and choking-related events associated with psyllium laxatives in all dosage forms, not granular dosage forms alone (Ref. 6). This review found 98 total adverse events. Of the four deaths reported, only one death was related to a psyllium laxative in a granular dosage form, swallowed unchewed with liquid. However, significantly more esophageal obstruction and choking-related events (78 out of 98) were associated with the granular dosage form compared to the powder or wafer dosage form (68 FR 46133 at 46135), and these events frequently required medical intervention (59 out of 78). Only 13 out of the 98 choking-related and esophageal obstruction events were reported for a leading psyllium laxative in powder dosage form. Only 2 of these 13 events were confirmed cases of esophageal obstruction, where a mass blocking the esophagus was actually visualized. The two events involved subjects who, along with a psyllium laxative in powder dosage form, took an additional medicine (contrast medium tablets or a pain relief caplet), which was later found in the blocking mass. In comparison, most of the events associated with the psyllium laxatives in granular dosage form (59 out of 78) were confirmed cases of esophageal obstruction, requiring medical intervention to relieve the obstruction. None of the esophageal obstruction cases associated with psyllium laxatives in granular dosage form mentioned an additional medicine being taken as a complicating factor.

FDA subsequently requested an update of adverse events associated with psyllium laxatives in granular dosage form from a major manufacturer of these products. This manufacturer reported 43 events of esophageal obstruction associated with the company's psyllium products in granular dosage form occurring between January 1999 and January 2001 (Ref. 7). In May 2002, FDA searched the AERS database for events of esophageal obstruction that had occurred since the previous search in October 2000, and found one additional event caused by this same psyllium product in granular dosage form (Ref. 8). These more recent events occurred despite labeling changes initiated by the manufacturer,

as well as labeling required by FDA (§ 201.319).

FDA concludes that this safety risk posed by psyllium laxatives in granular dosage form outweighs the benefits of these products. To support its claim that FDA failed to consider the benefits of psyllium laxatives in granular dosage form, the comment contended that granular dosage forms are preferred by consumers over powder and other forms. However, many other OTC laxative drug products are available that have the same purpose as psyllium products in granular dosage form but without the associated danger of esophageal obstruction.

FDA finds that the study by Marlett et al. (Ref. 3) submitted by the comment does not contribute any new data to support the safety of psyllium laxative products in granular dosage form. The article reports the results of a placebo-controlled, single-blind study comparing the effectiveness of two psyllium-containing laxatives, a granular dosage form containing psyllium plus senna and a powder dosage form containing psyllium only. FDA believes that any results suggesting that the granular dosage form is more effective than the powder dosage form are confounded by the comparison of products with different active ingredients—psyllium plus senna combined versus psyllium only. FDA reviewed the study for information relating to product safety. Only a few nonserious adverse events are reported for either treatment group. The small number of subjects (42) precludes any conclusions about the safety of either formulation in the general population.

FDA concludes that the submitted foreign safety data (Refs. 4 and 5), a total of 16 events that occurred outside the United States since 1980, do not add any significant evidence to support the safety of psyllium laxatives in granular dosage form. The comment reported three serious and five nonserious cases of dysphagia and/or esophageal obstruction following use of the company's psyllium and senna combination product in granular dosage form. The comment also reported six serious and two nonserious events for its psyllium-only product in granular dosage form. According to the comment, none of these events resulted in death or serious injury, and all of the people recovered. The comment claims these products are leading laxatives in Europe and this small number of serious adverse events demonstrates their safety. FDA finds the data inadequate to make any conclusion on safety. Further, FDA believes the data collected within the United States provides sufficient

basis for a safety concern, without the need for additional consideration of foreign safety data.

III. FDA's Final Conclusions on OTC Laxative Products in Granular Dosage Form Containing Psyllium Ingredients

FDA finds that OTC laxative drug products in granular dosage form containing psyllium present an unnecessary risk of esophageal obstruction and choking. These serious medical emergencies continue to occur despite previous measures taken to promote safe use of these products, including required warning and direction statements in § 201.319 for all OTC drug products containing water-soluble gums, hydrophilic gums, or hydrophilic mucilloids as active ingredients, including psyllium ingredients in granular dosage form. These statements instruct consumers to take adequate fluid and to avoid using the product if the person has previously experienced any difficulty in swallowing.

FDA is reclassifying bulk laxatives in granular dosage form containing psyllium ingredients from Category I (monograph) to Category II (nonmonograph). FDA is adding granular dosage forms containing psyllium ingredients to § 310.545(a)(12)(i) (21 CFR 310.545(a)(12)(i)), which lists those active ingredients currently without adequate data to establish general recognition of safety and effectiveness as a bulk laxative. Concurrently, FDA is revising § 201.319 to specifically exclude laxative drug products in granular dosage form containing psyllium ingredients. FDA concludes that the warnings and directions statements required in § 201.319 are not adequate to provide for the safe and effective use of psyllium products in granular dosage form. This final rule applies to OTC psyllium laxative drug products in granular dosage form that include, but are not limited to, any granules that are: (1) Swallowed dry prior to drinking liquid, (2) dispersed, suspended, or partially dissolved in liquid prior to swallowing, (3) chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid, or (4) sprinkled over food.

Part of an August 5, 2003, proposed rule for OTC laxative drug products proposes to exclude psyllium ingredients when contained in granular dosage forms from the list of GRASE bulk-forming psyllium laxative active ingredients in § 334.10 (21 CFR 334.10). We will finalize this part of the proposed rule to exclude psyllium ingredients when we publish the final

monograph for OTC laxative drug products.

Accordingly, any OTC laxative drug product in granular dosage form that contains psyllium is considered not GRASE and misbranded under section 502 of the act (21 U.S.C. 352). This type of drug product is 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 (21 CFR part 314), is required for marketing. This final rule applies to any OTC psyllium-containing laxative drug product in granular dosage form that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule. Further, any OTC drug product that was previously initially introduced or initially delivered for introduction into interstate commerce cannot then be repackaged or relabeled after the effective date of this final rule.

IV. Analysis of Impacts

In accordance with Executive Order 12866, FDA has previously analyzed the potential economic effects of this final rule (68 FR 46133 at 46136). As announced in the proposal, the agency has determined that the rule is not a significant regulatory action as defined by the Order. The agency has not received any new information or comments that would alter its previous determination.

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of the rule on small entities. Because of the limited number of products affected by this final rule, FDA does not believe that the final rule would have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written

statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The purpose of this final rule is to establish conditions under which OTC bulk-forming laxatives in granular dosage form containing psyllium ingredients are not generally recognized as safe and effective. At the time this rule was proposed, FDA's drug listing system (DLS) identified nine marketed OTC laxative drug products in granular dosage form containing psyllium ingredients, and FDA was aware of at least one other product not in its DLS. One manufacturer marketed three stock keeping units (SKUs) (individual products, packages, and sizes) of the granular dosage form. This manufacturer has since reformulated its products and, therefore, will not incur any new costs under this final rule. Two manufacturers marketed two SKUs each, and one manufacturer marketed one SKU. This final rule will result in the reformulation or removal of probably less than 10 products.

• Reformulation Costs

Some manufacturers may elect not to reformulate (i.e., they may elect to discontinue marketing of the product). For those products that need reformulation, the cost can be significant. The cost to reformulate a product will vary greatly depending on the nature of the change in the formulation, the product, the process, and the size of the firm. A manufacturer may elect to change the dosage form of the psyllium product or to substitute other monograph ingredients. This would require the manufacturer to redo the validation (product, process, new supplier), conduct stability tests, change master production records in order to insure compliance with current good manufacturing practice, and, for some dosage forms, conduct palatability tests. (See section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B) and 21 CFR parts 210 and 211.) FDA estimates the cost of reformulation to range from \$100,000 to \$500,000 per product. Therefore, if 10 products are reformulated, the midpoint of the cost estimate implies total costs of \$3,000,000. However, FDA believes

the total costs will be much smaller because not all manufacturers will elect to reformulate and some may choose to discontinue a product line if sales are too low to justify the added cost, and/or they also produce substitute products that do not require reformulation. Also, the major U.S. manufacturer of psyllium laxatives in granular dosage form has already reformulated its products and will not incur any new costs due to this final rule. Manufacturers may also elect to purchase reformulated products from another manufacturer and then be a distributor of that product. Competitive market forces and increased public awareness of a potential safety hazard of these bulk-forming psyllium laxatives in granular dosage form would most likely lead all manufacturers to move to alternative products over time.

- **Relabeling Costs**

Manufacturers of these products will also incur costs to relabel their products to reflect the new formulation. Estimates of relabeling costs vary greatly and range from \$3,000 to \$5,000 per SKU depending on whether the products are nationally branded or private label. FDA estimates that manufacturers with more than one affected SKU will likely discontinue one or more SKUs. If some SKUs are discontinued, FDA estimates that only approximately three SKUs will need to be relabeled as a result of reformulation. If these SKUs are relabeled, the total one-time cost of relabeling is about \$9,000 (three SKUs x \$3,000) to \$15,000 (three SKUs x \$5,000). This relabeling cost should not be a significant economic impact on a substantial number of small entities.

Some manufacturers may choose to submit an NDA deviation for their psyllium product in accordance with 21 CFR 330.11. Overall, there may be fewer costs incurred by this process than by submission of a full NDA.

Because these products must be manufactured in compliance with pharmaceutical current good manufacturing practices (21 CFR parts 210 and 211), all firms currently have the necessary skills and personnel to perform the tasks of reformulation, validation, and relabeling either in-house or by contractual arrangement. This rule will not require any new reporting and recordkeeping activities. No additional professional skills are needed.

- **Regulatory Alternatives Considered**

FDA considered but rejected the following alternatives: (1) Leave these products in the monograph, and (2) an exemption from coverage for small entities. FDA does not believe that these or other alternatives to this final rule

would adequately provide for the safe use of these OTC drug products.

Based on the foregoing, FDA does not believe that this final rule would have a significant economic impact on a substantial number of small entities. However, FDA recognizes the uncertainty of its estimates with respect to the number of affected small entities and products, as well as the economic impact of the rule on those small entities. Thus, this economic analysis, together with other relevant sections, serves as FDA's final regulatory flexibility analysis.

V. Paperwork Reduction Act of 1995

FDA concludes that any relabeling required by this final rule is not subject to review by the Office of Management and Budget because it does not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the relabeling statements are in the TFM for OTC laxative drug products (50 FR 2124 and 51 FR 35136) and are a "public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

FDA has determined under 21 CFR 25.31(a) 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.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule will have a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Section 751 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that:

* * * no State or political subdivision of a State may establish or continue in effect any requirement-- * * * (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or

503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*).

* * *

Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See Section 751(b) through (e) of the act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.) This final rule will establish that OTC laxative drug products in granular dosage form containing bulk-forming psyllium ingredients are not GRASE and are misbranded. Although this final rule would have a preemptive effect, in that it would preclude States from promulgating requirements related to OTC laxative drug products in granular dosage form containing psyllium ingredients that are different from or in addition to, or not otherwise identical with the requirements in this final rule, this preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise. See *Geier v. American Honda Co.*, 529 US 861 (2000).

FDA believes that the preemptive effect of the final rule would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that "when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings." FDA provided the States with an opportunity for appropriate participation in this rulemaking when it sought input from all stakeholders through publication of the proposed rule in the **Federal Register** of August 5, 2003 (68 FR 46133). FDA received no comments from any States on the proposed rulemaking.

In addition, on February 13, 2007, FDA's Division of Federal and State Relations provided notice via fax and e-mail transmission to elected officials of State governments and their representatives of national organizations. The notice provided the States with further opportunity for input on the rule. It advised the States of the publication of the August 5, 2003, proposed rule and encouraged State and

local governments to review the notice and to provide any comments to the docket (Docket No. 1978N-0036L) by a date 30 days from the date of the notice (i.e., by March 14, 2007), or to contact certain named individuals. FDA received no comments in response to this notice. The notice has been filed in Docket No. 1978N-0036L.

In conclusion, FDA believes that it has complied with all of the applicable requirements under the Executive order and has determined that the preemptive effects of this rule are consistent with Executive Order 13132.

VIII. References

The following references are on display in the Division of Dockets Management (see ADDRESSES), under Docket No. 1978N-0036L, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

- 1. Adverse Event Reports from 1966 to 2000 for Psyllium Laxative Products (Perdiem, Metamucil, and Serutan) collected by FDA's Office of Compliance, in OTC vol. 090TFM6.
2. Comment No. C00206, Attachment 1.
3. Comment No. C00206, Attachment 3.
4. Comment No. C00206, Attachment 4.
5. Comment No. C00206, Attachment 5.
6. FDA, Office of Postmarketing Drug Risk Assessment (OPDRA)(Project ID (PID) 000607) regarding Psyllium Laxative Products Associated with Esophageal Obstruction and Choking, November 17, 2000, in OTC vol. 090TFM6.
7. Adverse Event Reports from January 1999 to January 2001 for Overnight Relief PERDIEM and Fiber Therapy PERDIEM collected by FDA's Office of Compliance in January 2001, in OTC vol. 090TFM6.
8. FDA, OPDRA Postmarketing Safety Review (PID D020201) regarding Senokot and Psyllium Laxative Products Associated with Esophageal Obstruction and Choking, May 15, 2002, in OTC vol. 090TFM6.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, 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 parts 201 and 310 are amended as follows:

PART 201—LABELING

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.319 is amended by revising paragraph (a) 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 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. 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. Granular dosage forms containing psyllium are not generally recognized as safe and effective as OTC laxatives (see § 310.545(a)(12)(i)(B) of this chapter) and may not be marketed without an approved new drug application because the warnings and directions in paragraph (b) of this section have been found inadequate for these products.

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PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

2. Section 310.545 is amended by redesignating paragraph (a)(12)(i) as paragraph (a)(12)(i)(A), by adding paragraph (a)(12)(i)(B), by revising paragraph (d) introductory text and paragraph (d)(1), and by adding paragraph (d)(38) to read as follows:

310.545 Drug products containing active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(12) * * *

(i)(B) Bulk laxatives—Approved as of March 29, 2007.

Granular dosage forms containing psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), psyllium seed husks, plantago husks, or plantago seed including, but not limited to, any granules that are:

(1) Swallowed dry prior to drinking liquid,

(2) Dispersed, suspended, or partially dissolved in liquid prior to swallowing,

(3) Chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid, or

(4) Sprinkled over food.

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(38) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3)(i), (a)(4)(i), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i)(A), (a)(12)(ii) through (a)(12)(iv)(A), (a)(14) through (a)(15)(i), (a)(16) through (a)(18)(i)(A), (a)(18)(ii) (except as covered by paragraph (d)(22) of this section), (a)(18)(iii), (a)(18)(iv), (a)(18)(v)(A), and (a)(18)(vi)(A) of this section.

* * * * *

(38) October 1, 2007, for products subject to paragraph (a)(12)(i)(B) of this section.

Dated: March 20, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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