

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). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by state, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

FDA believes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditures that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this proposed rule is to establish conditions under which OTC bulk-forming laxative psyllium ingredients in a granular dosage form are not generally recognized as safe and effective. FDA's drug listing system (DLS) identifies nine currently marketed OTC laxative drug products containing psyllium ingredients in granular dosage form and FDA is aware of at least one other product not in its DLS. One manufacturer currently markets three stock keeping units (SKUs) (individual products, packages, and sizes) of the granular dosage form that requires the product to be swallowed dry while drinking liquid; two manufacturers market two SKUs each, and one manufacturer markets one SKU. It is likely that there may be a few additional products that are currently not included in FDA's DLS. This proposed rule, when finalized, will result in the reformulation or removal of probably less than a dozen 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 good manufacturing practice, and, for some dosage forms, conduct palatability tests. (See section 501(a)(1)(B) of the act (21 U.S.C. 351(a)(1)(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. 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 ingredients in a 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 three to six SKUs will need to be relabeled as a result of reformulation. If these SKUs are relabeled, the total one-time cost of relabeling could range from \$9,000 (three SKUs x \$3,000) to \$30,000 (six SKUs x \$5,000). This relabeling cost should not be a significant economic impact on a substantial number or small entities.

Some manufacturers may choose to submit an NDA deviation for their psyllium product in accordance with § 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 the pharmaceutical current good manufacturing practices (21 CFR parts 210 and 211), all firms have the necessary skills and personnel to perform the tasks of reformulation, validation, and relabeling either in-house or by contractual arrangement. The 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 additional alternatives: (1) Leave these products in the monograph, and (2) an exemption from coverage for small entities. FDA does not consider either of these approaches acceptable because they do not assure that consumers will have safe OTC psyllium laxative drug products in a granular dosage form. FDA does not believe that there are any significant alternatives to the proposed rule that would adequately provide for the safe use of these OTC drug products.

FDA does not believe that this proposed 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 initial regulatory flexibility analysis.

Finally, FDA specifically invites public comment regarding any substantial or significant economic impact that this proposed rule would have on OTC laxative drug products containing psyllium ingredients in a granular dosage form. Types of impact may include, but are not limited to, the costs associated with reformulation, relabeling, or repackaging. Comments regarding the impact of this rulemaking on OTC laxative drug products containing these ingredients should be accompanied by appropriate documentation. FDA is providing a period of 90 days from the date of publication of this proposed rule in the **Federal Register** for comments on this subject to be developed and submitted. FDA will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.