

(400) of the affected products are antidiarrheal drug products that contain bismuth subsalicylate as the active ingredient. The cost to implement the new Reye's syndrome warning for those products is significantly mitigated because the warning will be incorporated into the new labeling for those products as a result of publication of the final monograph for OTC antidiarrheal drug products.

The remaining 2 percent (100) of affected products includes OTC drug products containing aspirin and nonaspirin salicylates marketed under an NDA or ANDA or marketed under the tentative final monograph for OTC overindulgence drug products. A number of the overindulgence drug products that contain bismuth subsalicylate as the active ingredient also bear antidiarrheal claims and, thus, will need to be relabeled as a result of publication of the final monograph for those drug products. The cost to add a warning to product labeling generally averages about \$2,000 to \$3,000 per SKU. Thus, the cost for these products to be relabeled is estimated to be between \$200,000 and \$300,000.

#### C. Small Business Impacts

Census data provide aggregate industry statistics on the total number of manufacturers for Standardized Industrial Classification Code 2384 Pharmaceutical Preparations by establishment size, but do not distinguish between manufacturers of prescription and OTC drug products. According to the U.S. Small Business Administration (SBA) designations for this industry, however, over 92 percent of the roughly 700 establishments and over 87 percent of the 650 firms are small. (Because census size categories do not correspond to the SBA designation of 750 employees, these figures are based on 500 employees.)

The agency's drug listing system indicates that between 900 and 1,500 marketers will need to relabel as the result of this final rule. Thus, the agency believes that many of the manufacturers affected by this final rule would be small. However, the cost of relabeling of private label products is incurred by the private label manufacturers, not the individual small marketers. The effect on individual firms will vary with the number of the firm's SKUs that require relabeling and the size and cost of the firm's labeling inventory. Most small firms will not incur significant regulatory costs because they manufacture few affected SKUs and use less expensive labeling stock. Because most firms will be able to incorporate these required changes when

incorporating other regulatory requirements, this final rule should have a minimal economic impact on small entities.

#### D. Alternatives

The agency considered and rejected a more costly alternative that would have required all products to be relabeled within 12 to 18 months of publication of this final rule in the **Federal Register**, with a multimillion dollar cost to industry based on the potential number of affected products. Because 80 percent of the products (a number of which have multiple SKUs) already have a Reye's syndrome warning on their label, the agency concluded that the incremental benefits of a reworded warning did not outweigh the costs. As discussed in section II, comment 11 of this document, the agency has set the implementation date of this final rule for the Reye's syndrome warning for OTC antidiarrheal drug products that contain bismuth subsalicylate as an active ingredient to coincide with the compliance dates for the final monograph for those drug products. The agency considers this a reasonable time for manufacturers to implement these final rules, and the costs associated with implementation will be less for one label change than for two label changes. The agency has also set the compliance dates for the majority of the products (internal analgesic, antipyretic, and antirheumatic) affected by this final rule to coincide with the final monograph for those drug products, to be published in the future. The agency encourages manufacturers to relabel their products voluntarily, if new labeling is implemented before that final monograph publishes.

The agency considered, but rejected, an exemption from coverage for small entities because the new labeling information is also needed by consumers who purchase products marketed by those entities. However, longer compliance dates are being provided for antidiarrheal and overindulgence drug products containing bismuth subsalicylate with annual sales less than \$25,000 (an additional 12 months) and for products containing aspirin and nonaspirin salicylates marketed under an NDA or ANDA (an additional 6 months).

#### E. Conclusion

The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this final rule, because the final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The

current inflation adjusted statutory threshold is about \$110 million.

This analysis shows that the agency has considered the burden to small entities and provided compliance dates that should significantly reduce the burden. Thus, the agency certifies that this final rule will not have a significant impact on a substantial number of small entities.

#### V. Paperwork Reduction Act of 1995

FDA concludes that the warning statement set forth in 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 required labeling is 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

The agency 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 does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

#### VIII. References

The following references are on display in the Dockets Management Branch (*see* section I of this document) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Halpin, T. et al., "Reye's Syndrome and Medication Use," *Journal of the American Medical Association*, 248:687-723, 1982.
2. Hurwitz, E. et al., "Public Health Service Study of Reye's Syndrome and Medications: Report of the Pilot Study," *New England Journal of Medicine*, 313:849-857, 1985.