

included in 21 CFR part 343 in the final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products and in part 357, subpart J, in the final monograph for OTC overindulgence drug products, when the monographs for those products are finalized. Other labeling that was proposed in § 357.950 for drug products for the relief of symptoms associated with overindulgence in food and drink will be finalized in a future issue of the **Federal Register**. The OTC drug product labeling format and content requirements in § 201.66(c)(5)(ii)(A) state that the warning in § 201.314(h)(i) shall follow the subheading "Reye's syndrome:".

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 so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs 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 these 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. This judgment balances the benefits of these drug products against their potential risks (*see* 21 CFR 330.10(a)).

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).

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). 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). 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). The rules that led to the development of this final rule were published in 1993, before the Unfunded Mandates Reform Act of 1995 was enacted. The agency explains in this final rule that the final rule will not 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.

The agency concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This final 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 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.

The purpose of this final rule is to revise the Reye's syndrome warning that is already required for OTC drug products that contain aspirin for use by children and adolescents and to extend the requirement to those products that contain nonaspirin salicylates (including bismuth subsalicylate) as active ingredients. The revised warning is similar to the voluntary warning already included on some OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate. This final rule is intended to bring uniformity and consistency to the labeling of OTC drug products containing aspirin and nonaspirin salicylates.

A. Benefits

The revised warning will inform consumers of the symptoms of Reye's syndrome and advise that aspirin or nonaspirin salicylate (including bismuth subsalicylate) drug products should not be given to children or

teenagers who have or are recovering from chicken pox or flu-like symptoms. As stated in the October 1993 proposed rule (58 FR 54228), the agency has reconsidered the need to include all OTC drug products containing salicylates in this required warning. Fifteen adverse drug reports linking bismuth subsalicylate with Reye's syndrome have been entered into the agency's database since March 1991, when the first Reye's syndrome death associated with bismuth subsalicylate was reported to the agency (Refs. 8 and 18). Most of these cases occurred in children, and deaths were reported in the majority of these cases.

FDA cannot quantify the expected benefits of this rule, because it lacks the data to conduct a quantitative risk assessment. The agency notes, however, that in most disease surveillance systems, reported cases are recognized to represent only a fraction of the actual total. Reye's syndrome is manifested by a change in mental status ranging from lethargy to delirium, seizures, and respiratory arrest (Ref. 19). Mortality is related to the stage of coma at the time of hospital admission and has been estimated to be as high as 40 percent (Ref. 19). It has been estimated that 30 percent of Reye's syndrome patients who deteriorate to the stage of neurologic seizure, and survive, develop serious neurologic sequelae. Thus, alerting consumers to the early symptoms of Reye's syndrome is essential so that prompt medical treatment can be obtained, with a better prognosis for the patient.

B. Costs

Based on information in the agency's drug listing system, there are between 900 and 1,500 manufacturers and distributors that together produce about 5,000 OTC drug products containing salicylates as an active ingredient that will be affected by this final rule. Over 90 percent of these products are internal analgesic, antipyretic, and antirheumatic drug products, which may have more than one stock keeping unit (SKU) (individual products, packages, and sizes). Because the majority of the products already include a warning statement that is similar to the labeling required by this final rule, most changes will be minor. Further, the cost to implement the new warning statement should be negligible because the agency is providing that the warning can be coordinated with the other labeling changes that will be included in a future final monograph for those products.

As discussed elsewhere in this issue of the **Federal Register**, about 8 percent