

The agency disagrees with the comment that a doctor's advice to take an aspirin-containing drug in limited circumstances will be undermined or that consumers will be frightened from using the drug at the direction of a doctor if the revised Reye's syndrome warning is used in the product's labeling. Salicylates (including aspirin) should not be given to, or used by, children and teenagers who have or are recovering from certain viral illnesses. In most conditions for which aspirin is indicated there are alternative medications that doctors can recommend. In rare instances where other medications are contraindicated, a patient's doctor may determine that the benefits of aspirin use outweigh the risks. In those cases, it is still possible for the doctor to override the label warning if, in his or her judgment, aspirin should be used. The agency believes the revised warning continues to reflect the agency's 1982 position.

(Comment 9) One comment recommended that the agency modify the proposed warning to include "while using this medication" as follows: "If nausea, vomiting, or fever occur while using this medication, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness." The comment stated that reference to indications and adverse effects that are similar may be confusing to consumers, who may assume that the presence of nausea, vomiting, or fever alone is an absolute indication of Reye's syndrome. The comment suggested this change would convey a clearer message that this drug, when used to treat the symptoms of a viral illness in children and teenagers, may precipitate Reye's syndrome.

The agency does not believe the proposed warning suggests that any individual symptom is an absolute indication of Reye's syndrome. However, the agency has deleted "fever" and added "changes in behavior" to the list of symptoms to more accurately reflect the symptoms associated with the development of Reye's syndrome. (See section II, comment 5 of this document.) The agency is adding the phrase "when using this product" to convey a clearer message that the drug, when used to treat the symptoms of a viral illness, may precipitate Reye's syndrome.

(Comment 10) Noting that pediatric nurse practitioners have been a source of primary health care to children and teens for over 25 years, one comment suggested amending the proposed Reye's syndrome warning by replacing "doctor" with "health-care professional."

The agency agrees with the comment that health care professionals play important roles in delivering clinical services directly to consumers and may sometimes serve as primary medical care providers. However, because of the serious consequences of Reye's syndrome the agency believes that a doctor should be consulted if symptoms associated with Reye's syndrome (e.g., changes in behavior with nausea and vomiting) occur after taking a salicylate. In addition, the agency believes that the use of the term "doctor" is consistent with other OTC drug product labeling warnings. As discussed in the OTC labeling requirements final rule (64 FR 13254 at 13261, March 17, 1999), the agency determined that questions related to certain conditions and symptoms are best answered by a doctor who is trained and licensed specifically to make a differential diagnosis and to treat disease entities. Therefore, the agency is retaining the term "doctor" in the warning.

(Comment 11) Two comments stated that due to economic hardship, 6 months was too short to revise labels, dispose of existing label stock, relabel product, and initiate the distribution process. Therefore, one comment requested that the agency consider an 18-month implementation date instead of the proposed 6 months. Another comment requested 12 months. One comment stated that labeling changes could be made more efficiently if multiple rulings for similar products become effective simultaneously. The comment suggested that the agency incorporate all revisions into the final monograph for OTC internal analgesic drug products to decrease costs.

The agency agrees with the comments that 6 months may not be a reasonable amount of time for manufacturers to implement the required warning for salicylate-containing drug products. The labeling for most OTC drug products (those containing aspirin) covered by this final rule already includes a Reye's syndrome warning similar to the warning in this final rule, and most manufacturers would need to make only minor labeling revisions. Because of the large number of affected products and because many of these products are internal analgesics that contain aspirin and already have a Reye's syndrome warning, the agency is providing that the compliance dates for those products to incorporate the new warning will be established when the final monographs for OTC internal analgesic, antipyretic, and antirheumatic drug products and OTC menstrual drug products are published in a future issue of the **Federal Register**. Thus, all of the

labeling revisions required by those final monographs and the new Reye's syndrome warning can be implemented at the same time. The agency currently expects those final monographs or portions of the final monographs to publish within the next 18 to 24 months. Thus, any economic hardship on manufacturers of these products is greatly reduced or eliminated.

Manufacturers of OTC antidiarrheal drug products have 12 or 24 months to implement the new Reye's syndrome warning, which will be done concurrently with implementation of the labeling in the final monograph for those drug products, published elsewhere in this issue of the **Federal Register**. Because the Reye's syndrome warning is only one small part of the labeling for OTC antidiarrheal drug products containing bismuth subsalicylate, the agency is requiring all labeling for those products to be implemented at the same time. Manufacturers of OTC overindulgence drug products also have 12 or 24 months to implement the new Reye's syndrome warning. Because the agency does not currently expect the final rule for those products to publish in the next 18 to 24 months, it is requiring those products to include the Reye's syndrome warning before the final monograph is published. There are a limited number of affected products in this product category, and any economic costs for manufacturers of those products should be minimal. All manufacturers are encouraged to incorporate this new warning information into product labeling if they print new labeling before the required implementation times.

Although this final rule may have an economic impact on a few manufacturers, the agency concludes that the potential benefits of the rule, including reduced risk of adverse effects, override these economic concerns. (See section II, comment 1 of this document.)

III. The Agency's Final Conclusions

The agency has determined that the Reye's syndrome warning should apply to all oral and rectal OTC drug products containing salicylates as active ingredients, regardless of their intended use. Therefore, the requirement for a Reye's syndrome warning for aspirin and nonaspirin salicylates (including bismuth subsalicylate) will appear in one location (§ 201.314(h)). A reference to this warning is included in § 335.50(c)(2)(i)(A) (21 CFR 335.50(c)(2)(i)(A)) of the final monograph for OTC antidiarrheal drug products. A reference will also be