

products. Listing the early symptoms of Reye's syndrome will help alert consumers to contact a doctor during the early stages of the syndrome, when a better outcome is expected.

(Comment 5) Noting that the medical literature demonstrates that fever is not a symptom of Reye's syndrome, two comments recommended that the agency modify the proposed warning by deleting "fever" from the list of Reye's syndrome symptoms. The comments also cited a conclusion from the National Institutes of Health Consensus Development Conference (Ref. 16) that "neither fever nor jaundice is usually present" as a symptom of Reye's syndrome.

One comment stated that the proposed list of Reye's syndrome symptoms is incomplete because important symptoms (e.g., lethargy, confusion, aggressiveness) were not included. The comment noted that by omitting some important symptoms from the list, parents may not seek emergency treatment for a child with Reye's syndrome. The comment added that the proposal overwarns by including fever, and parents may call a doctor whenever a fever is present.

Fever is not a generally recognized symptom of Reye's syndrome. Thus, the term "fever" is being deleted from the proposed warning. While nausea and vomiting are easily recognizable, early symptoms of Reye's syndrome, the agency agrees with the comment that adding other associated symptoms would more accurately reflect the situation in which parents and young people need to be concerned about the possibility of Reye's syndrome. The agency has also considered that label space is limited and believes the broad term "changes in behavior" is understood by consumers and covers the symptoms mentioned by the comment. When changes in behavior are associated with nausea and vomiting it is important to seek medical care as soon as possible. Therefore, the warning statement includes the phrase, "if changes in behavior with nausea and vomiting occur."

(Comment 6) One comment contended that there is no scientific evidence of an association between Reye's syndrome and the use of aspirin by children and teenagers who "are recovering from" chicken pox, flu, or flu symptoms. The comment stated that while a warning about the recovery period from a preceding illness may be appropriate for products used to treat, and possibly mask, the early symptoms of Reye's syndrome, such a warning on aspirin is not supported by the studies that have been reported to show an

association with aspirin. Further, such a warning is inconsistent with the message repeatedly given to the public that aspirin should not be used for the symptoms of flu or chicken pox.

The comment stated that the studies used by FDA to support the regulation provide no evidence that aspirin taken while recovering from chicken pox or flu (but not for chicken pox or flu symptoms themselves) increases the risk of Reye's syndrome. Unless further studies show that there is a risk in taking aspirin for situations other than the symptoms of flu or chicken pox, the comment contended there is no basis for the proposed change. Any use of aspirin while "recovering from" these illnesses would be for residual symptoms of chicken pox or flu and therefore would be covered by the current warning.

The agency disagrees with the comment. As stated in the agency's May 1993 proposed rule (58 FR 26886 to 26887), Reye's syndrome most commonly occurs following influenza, chicken pox, and several other common viral infections. As symptoms of the initial viral illness begin to diminish or clear, the dramatic symptoms of Reye's syndrome (i. e., intractable vomiting, lethargy, or delirium) begin (Ref. 17). It is not clear that aspirin or other salicylate use in children is safe at any time from onset to complete recovery from the initial viral illness. Some of the residual symptoms, including fever, associated with the initial viral illness may still be present at the time that symptoms of Reye's syndrome develop. Although fever is not usually a symptom of Reye's syndrome and aspirin is not used to treat the symptoms of Reye's syndrome, it may be used to treat lingering symptoms of the initial viral illness in some people. Thus, the agency believes it is important that aspirin and other salicylates not be given to children and teenagers when flu symptoms are present or when the symptoms are disappearing and the child seems to be recovering from the illness (58 FR 26886 at 26887). The warning for OTC aspirin drug products should be consistent with that for other salicylates and include a broad warning not to use the product both during the illness and during recovery. Therefore, the agency is retaining the proposed phrase "who have or are recovering from" in this final rule.

(Comment 7) Two comments recommended that the word "flu" not be included in the proposed Reye's syndrome warning. One comment noted that, in issuing the current aspirin label regulation in 1988, FDA refused to expand the warning beyond "chicken pox or flu symptoms," based on the PHS

study on which it relied for scientific justification for the warning requirement. The comment asserted that adding the word "flu" would provide no new information and may confuse consumers who are unable to differentiate "flu" from flu symptoms. The other comment recommended that the words "flu symptoms" not be included in the warning because they are redundant and likely to confuse consumers. The comment recommended that the agency use only one of these in the warning.

The agency disagrees with the comments that use of the words "flu symptoms" along with the word "flu" is redundant, but agrees that including both in the warning may confuse some consumers who may be unable to differentiate "flu" from "flu symptoms." Therefore, the agency is replacing "flu" and "flu symptoms" with "flu-like symptoms," as this description broadens the warning to help consumers who may not be sure the symptoms are due to the flu.

(Comment 8) One comment asserted that the proposed amendment would remove the reference to consult a doctor, and would significantly undermine a doctor's ability to prescribe aspirin under certain circumstances despite the reported risk of Reye's syndrome. The comment stated that the proposed warning simply directs children and teenagers not to use the drug, whereas the current warning cautions against use "before a doctor is consulted about Reye's syndrome." Further, while there may be no conditions for which bismuth subsalicylate should be used in children or teenagers having chicken pox or flu symptoms, aspirin has other important uses that might justify a physician's recommendation that it be used, despite the warning. The comment explained that if a doctor believes that a child suffering from the pain and disability of juvenile rheumatoid arthritis should use aspirin, and the benefits outweigh the risks, the doctor should be able to make a patient-specific assessment of risks, and consumers should not be afraid to follow the doctor's advice. The comment concluded that without justification, it is inappropriate to reverse the reasoned position held by the agency in 1982 (47 FR 57886 at 57895, December 28, 1982) in which the suggested warning against salicylate use in children did not apply to all circumstances, but included the phrase "unless directed by a doctor." The agency stated that the possible benefits of salicylates might outweigh the risk of Reye's syndrome in certain cases such as juvenile rheumatoid arthritis.