

products containing nonaspirin salicylates, these products should bear a warning to alert consumers that children and teenagers recovering from chicken pox or flu-like symptoms should not use these products.

(Comment 2) Several comments contended that requiring a Reye's syndrome warning on the large number of drug products containing salicylates as inactive ingredients would reduce its effectiveness for products such as aspirin for which the warning is justified. The comments noted that salicylates are commonly used as flavorings in many OTC drugs, including mouth rinses, toothpastes, cough medications, stomach remedies, laxatives, stool softeners, and other mint-flavored oral medications. These flavorings impart a distinctive characteristic that cannot be readily duplicated using other ingredients.

The comments added that salicylates are used as buffers, stabilizing agents, and preservatives. Replacing salicylates with alternative excipients as buffering agents does not provide comparable hydrogen-ion concentration (pH) control, thereby increasing the risk of microbial contamination. Further, alternative buffering agents do not provide adequate suspension of the active ingredient, potentially leading to misdosing. The comments contended that practical replacements for salicylate excipients do not exist.

One comment concluded that the widespread presence of salicylates in prescription and OTC drugs, and foods, together with the very low reported incidence of Reye's syndrome in recent years, strongly suggests that exposure to nonaspirin salicylate inactive ingredients is not a risk factor for developing Reye's syndrome. The comment argued that a Reye's syndrome warning is not needed for drug products containing nonaspirin salicylates as inactive ingredients unless the products could be used to self-treat symptoms such as nausea, diarrhea, and vomiting (which may be early signs of Reye's syndrome). The comment projected a significant economic impact in the cost of relabeling drugs containing salicylates as inactive ingredients.

The agency discussed one report in the October 1993 proposed rule (58 FR 54228 at 54229) of Reye's syndrome associated with a drug product containing a nonaspirin salicylate as an inactive ingredient. This case resulted in the death of a child treated with a theophylline drug product that contained calcium salicylate as an emulsifying agent. The report provided minimal information. Other than this case report, the agency is not aware of

any data supporting an association of Reye's syndrome with salicylate inactive ingredients. The concentration of salicylates contained as inactive ingredients in OTC drug products is generally low and the mechanism of action responsible for the development of Reye's syndrome is unknown. Therefore, the agency does not have sufficient data and information at this time to require a Reye's syndrome warning on OTC drug products containing salicylates as inactive ingredients. In the event additional data become available on the association of salicylates, as inactive ingredients, with Reye's syndrome, the agency will reconsider this position.

(Comment 3) Several comments asserted that the use of the same warning for OTC drug products containing bismuth subsalicylate and aspirin is inappropriate. The comments stated that the purpose of the current voluntary warning on OTC overindulgence drug products containing bismuth subsalicylate is different from that for aspirin-containing OTC drug products, in that it is intended to discourage attempts to self-treat symptoms (nausea and vomiting) that may be early signs of Reye's syndrome. Because the intended uses for aspirin (minor aches and pains and fever) are different, the comments contended that the warnings should be different.

The agency agrees that the warning on bismuth subsalicylate products that mentions nausea and vomiting is helpful in discouraging self-treatment of symptoms that may be early signs of Reye's syndrome and in encouraging prompt medical attention. Likewise, people who take an aspirin product for aches and pains and fever related to the flu could also have nausea and vomiting. Regardless of the product's indication, the warning statement is intended to alert consumers when they should not use the products and that prompt medical attention should be sought if certain symptoms are present. Therefore, based on the information available suggesting that Reye's syndrome is associated with both aspirin and nonaspirin salicylates, the agency has determined that the warning statement in this final rule should be the same for all OTC drug products containing salicylates as an active ingredient.

(Comment 4) One comment urged the agency not to include Reye's syndrome symptoms on aspirin-containing products, asserting that this additional language is beyond the scope of traditional or appropriate label warnings, *i.e.*, providing sufficient

information for consumers' safe and effective use of an OTC drug product. The comment suggested that knowledge of Reye's syndrome symptoms may be important for the safe use of OTC drug products containing bismuth subsalicylate, but it is not needed for the safe and effective use of aspirin. Noting the agency's rejection of a recommendation to include symptoms in the Reye's syndrome warning in current § 201.314(h)(1) (*see* the March 7, 1986, final rule (51 FR 8180 at 8181)), the comment suggested that the agency's rationale still applies today. The comment further suggested that the listing of symptoms in the warning may cause consumers to believe that the common symptoms of nausea and vomiting or fever should prompt a call to a doctor.

Another comment suggested that the addition of nausea, vomiting, and fever to the Reye's syndrome warning is redundant because consumers are already familiar with these common symptoms of flu. Pointing out that the labeling type size is already small due to the amount of required label information, the comment asserted that this additional verbiage would decrease label readability and the conspicuousness of the warning.

The agency disagrees with the comment's assertion that including the symptoms in the warning is beyond the scope of traditional or appropriate OTC drug label warnings. Warnings for certain ingredients caution consumers to consult a doctor or to discontinue use of the product if specific symptoms appear. For example, the warning in § 340.50(c)(1) (21 CFR 340.50(c)(1)) alerts consumers of the specific symptoms of excessive caffeine consumption, stating in part: “\* \* \* too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.” A proposed warning for products containing aspirin and other salicylates states: “If ringing in the ears or a loss of hearing occurs, consult a doctor before taking any more of this product.” (*See* 53 FR 46204 at 46256, November 16, 1988.) Thus, symptoms have traditionally been included in warnings for certain OTC drug products.

As one comment noted, the agency rejected a recommendation for including symptoms in the Reye's syndrome warning in 1986. FDA has reconsidered this position, and now recognizes increased value in information on the symptoms of Reye's syndrome that can be particularly helpful to alert consumers of the potential situations where problems could arise with the use of these