

agency also proposed to extend the warning to OTC drug products containing nonaspirin salicylates, such as choline salicylate, magnesium salicylate, and sodium salicylate, but did not specify whether the warning would apply to products containing salicylates used as inactive ingredients.

In response to the two proposals, the agency received comments from two manufacturers and two professional associations. These comments are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 under Docket No. 82N-0166 or 93N-0182.

The agency has determined that the two proposals should be combined so that all Reye's syndrome warnings appear in one place (§ 201.314(h)(1)), with an appropriate cross reference in the individual ingredient monographs. Thus, there is no need for a separate rule for overindulgence drug products containing bismuth subsalicylate. This Reye's syndrome warning also applies to OTC antidiarrheal drug products containing bismuth subsalicylate because bismuth subsalicylate is a monograph ingredient for this use at this time.

In the proposed rules to amend parts 201 and 257 (21 CFR parts 201 and 357), the agency advised that any final rule based on the proposals will be effective 6 months and 12 months, respectively, after the date of publication in the **Federal Register**. The agency is setting the effective date for this final rule at 12 months, but is establishing varying compliance dates for this final rule. (See *Compliance Dates* in the **DATES** section and section II, comment 11 of this document.) Any OTC drug product that is subject to this final rule that is initially introduced or initially delivered for introduction into interstate commerce after the compliance dates for the rule will be considered misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(n) and 352(a) and (f)) if it does not contain the new warning required by this final rule. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the compliance dates of

the rule must comply with the rule regardless of the date that the product was initially introduced or initially delivered for introduction into interstate commerce.

## II. The Agency's Conclusions on the Comments

(Comment 1) One comment supported the agency's proposal to require a Reye's syndrome warning on products containing nonaspirin salicylates. Other comments asserted that there are no scientific data establishing an association between nonaspirin salicylates and Reye's syndrome. The comments argued that numerous epidemiological studies of the etiology of Reye's syndrome have failed to suggest an association with nonaspirin salicylates. One comment included published reports of the Ohio Department of Health study (Ref. 1), the Public Health Service (PHS) pilot and main studies (Refs. 2 and 3), and the Yale study (Ref. 4) and cited two reports from Australia published in 1987 (Ref. 5) and 1990 (Ref. 6). The comment also included unpublished data (Ref. 7) based on the Ohio Department of Health study and the PHS pilot study.

The comments contended that the low incidence of Reye's syndrome, in spite of widespread use of nonaspirin salicylates and the presence of naturally occurring salicylates in food, strongly argues against an association with nonaspirin salicylates. The comments added that the case reports associating Reye's syndrome with the use of bismuth subsalicylate, calcium salicylate, and choline salicylate cited in the proposal provided insufficient detail to support such an association. The comments also criticized the *in vitro* data cited by the agency and questioned whether mitochondrial swelling, seen in the presence of salicylates in the studies, is relevant to the pathogenesis of Reye's syndrome. One comment suggested that aspirin's acetylation mechanism may be responsible for the association between aspirin and Reye's syndrome.

The agency has reviewed the epidemiologic studies submitted by the comment and agrees that they did not find an association between nonaspirin salicylates and Reye's syndrome.

However, these studies lacked sufficient subjects to adequately evaluate such an association.

The PHS pilot study (Ref. 2) reported an association between Reye's syndrome and salicylate use, but did not differentiate between aspirin and other salicylates. In the main study (Ref. 3), the independent risk of Reye's syndrome with nonaspirin salicylates could not be assessed because only two cases were not exposed to aspirin. The Ohio Department of Health study (Ref. 1) reported a significant association between aspirin use and Reye's syndrome (relative risk 11.5; confidence interval 2.7 - 48.4;  $p < 0.001$ ). Further analysis (Ref. 7) of data from the second year of this study and the PHS pilot study showed that the Ohio study had a higher percentage of nonaspirin salicylate use in the Reye's syndrome cases than in the controls (25 percent versus 16.8 percent), whereas the findings for the PHS pilot study were mixed (14.8 percent versus 21.1, 31.6, and 12.7 percent). None of these findings were significant.

The agency notes that the Yale study (Ref. 4) investigated the validity of the reported association of aspirin and Reye's syndrome by evaluating potential bias associated with earlier studies. The authors concluded that there is a strong association between aspirin and Reye's syndrome, as reported in other studies, but the study did not evaluate the association of nonaspirin salicylates and Reye's syndrome. The two Australian studies mentioned by the comment (Refs. 5 and 6) did not show an association between salicylate ingestion (including aspirin) and Reye's syndrome.

The agency is aware of a number of reports linking bismuth subsalicylate-containing products to Reye's syndrome (Ref. 8). As of May 1999, the agency found 27 cases of potential neurologic reaction for these products reported from 1989 through 1997 in its Spontaneous Reporting System (SRS). Fifteen of these cases had a possible diagnosis of Reye's syndrome, and most of these were children. The remaining 12 cases (6 pediatric and 6 adult) included a variety of neurological disorders. Table 1 summarizes the 15 reports.

TABLE 1.—CASE REPORTS OF REYE'S SYNDROME OR SUSPECTED REYE'S SYNDROME IN PEOPLE WHO TOOK BISMUTH SUBSALICYLATE

FDA Number <sup>1</sup>	Age <sup>2</sup>	Gender <sup>3</sup>	Event (year)	Other drugs <sup>4</sup>	Outcome <sup>5</sup>
578534 and 725706	6Y	F	1989	APAP (only)	D
823003	P	M		U	U
823007 <sup>1</sup>	P	U	1985 or 1986	U	U
824682	P	F	1989	U	D