

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket Nos. 93N-0182 and 82N-0166]

RIN 0910-AA01

DMB

Display Date 4-16-03

Publication Date 4-17-03

Certifier A. Corbin

Labeling for Oral and Rectal Over-the-Counter Drug Products Containing Aspirin and Nonaspirin Salicylates; Reye's Syndrome Warning

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to amend its regulations to revise the Reye's syndrome warning required for oral and rectal over-the-counter (OTC) human drug products containing aspirin and to require a warning on OTC drug products containing nonaspirin salicylates as active ingredients. The revised warning will inform consumers of the symptoms of Reye's syndrome and advise that aspirin and nonaspirin salicylate drug products should not be given to children or teenagers who have or are recovering from chicken pox or flu-like symptoms. This final rule also finalizes FDA's notice of proposed rulemaking to require a Reye's syndrome warning for orally administered OTC drug products for relief of symptoms associated with overindulgence in food and drink (overindulgence drug products) that contain bismuth subsalicylate that published in the **Federal Register** of May 5, 1993 (58 FR 26886). FDA is issuing this final rule after considering public comment on the agency's notices of proposed rulemaking and all relevant data and information that have come to the agency's attention.

cd00185

82N-0166

93N-0182

NFR 1

DATES:

Effective Date: This final rule is effective [*insert date 12 months after date of publication in the **Federal Register***].

Compliance Dates: The compliance date for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales greater than \$25,000 is [*insert date 12 months after date of publication in the **Federal Register***]. The compliance date for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales less than \$25,000 is [*insert date 24 months after date of publication in the **Federal Register***]. The compliance date for OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under a new drug application (NDA) or abbreviated new drug application (ANDA) is [*insert date 18 months after date of publication in the **Federal Register***]. The compliance dates for all other OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under an OTC drug monograph (for internal analgesic, antipyretic, and antirheumatic drug products, or for menstrual drug products) will be established when the final monographs for those drug products are published in a future issue of the **Federal Register**.

FOR FURTHER INFORMATION CONTACT: Ida I. Yoder, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of May 5, 1993 (58 FR 26886), FDA published a notice of proposed rulemaking to require a Reye's syndrome warning for OTC overindulgence drug products that contain bismuth subsalicylate (the May 1993 proposed rule). The proposed warning stated: "Children and teenagers who have or are recovering from chicken pox, flu symptoms, or flu should NOT use this product. If nausea, vomiting, or fever occur, consult a doctor because these symptoms could be an early sign of Reye syndrome, a rare but serious illness." The agency did not propose this warning for OTC antidiarrheal drug products that contain bismuth subsalicylate because bismuth subsalicylate was not a proposed monograph ingredient for that use at that time.

This warning was intended to inform consumers of the earliest recognizable symptoms of Reye's syndrome and advise that OTC overindulgence drug products containing bismuth subsalicylate should not be used during the period when children or teenagers have, or are recovering from, the flu or chicken pox. The agency mentioned that it was considering revising the Reye's syndrome warning currently required for products containing aspirin in § 201.314(h)(1) (21 CFR 201.314(h)(1)) to be the same as the proposed warning for products containing bismuth subsalicylate.

In the **Federal Register** of October 20, 1993 (58 FR 54228), FDA published a notice of proposed rulemaking to revise the Reye's syndrome warning required for OTC drug products containing aspirin to be consistent with the proposed warning for OTC overindulgence drug products containing bismuth subsalicylate (the October 1993 proposed rule). The 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 ¹	Age ²	Gender ³	Event (year)	Other drugs ⁴	Outcome ⁵
578534 and 725706	6Y	F	1989	APAP (only)	D
823003	P	M		U	U
823007 ¹	P	U	1985 or 1986	U	U
824682	P	F	1989	U	D
824683	12Y	F		U	D
830479 ¹	between 8 and 15Y	U	1978	ASA	H
830513	U	U	1989	U	U
830516 ¹	between 8 and 15Y	U	1978	ASA	H
952481	6Y	M	1991	NR	D
957562	12Y	F	1992	ASA, D	D
958922	34M	F	1992	NR	D
947149	3Y	F	1993	NR	D
1502057 ¹	14Y	M	1994	APAP, CC	H
1623073	4Y	F	1995	APAP, D	D
1855719	2Y	M	1996	NR	D

¹ Also literature report

² M = months, Y = years, P = pediatric, U = unknown

³ F = female, M = male, U = unknown

⁴ ASA = aspirin, APAP = acetaminophen, CC = cough/cold preparation, D = diphenhydramine, NR = none reported, U = unknown

⁵ D = died, H = hospitalized, U = unknown

Because of the limited information available on these cases, it is not certain that bismuth subsalicylate was the cause of Reye's syndrome. However, most of the reports identified bismuth subsalicylate use only prior to the diagnosis of Reye's syndrome. Death was reported in 60 percent of the cases.

The agency notes that a recent report by Orłowski (Ref. 9) suggested that many people originally diagnosed with Reye's syndrome may have had metabolic disorders. To test this hypothesis, Orłowski evaluated the medical records of subjects in the Australian studies (Refs. 5 and 6) that had not shown an association with aspirin or salicylate ingestion and Reye's syndrome. The medical records of 26 people who were originally diagnosed with Reye's

syndrome and survived were reassessed using more precise diagnostic criteria. Eighteen (69 percent) of these were subsequently diagnosed as having other diseases (15 with inborn errors of metabolism). The most common metabolic disorder was medium-chain acyl-coenzyme-A dehydrogenase deficiency. Orłowski speculated that the disappearance of Reye's syndrome in the 1980s may be more related to the discovery of, and ability to diagnose, inborn errors of metabolism that mimic Reye's syndrome clinically, biochemically, and pathologically than to warning labels and the reduced use of aspirin. Although some people previously diagnosed with Reye's syndrome have been found to have metabolic disorders that may meet the criteria for a diagnosis of Reye's syndrome, and some people with metabolic disorders may be predisposed to developing Reye's syndrome, the agency finds there is no definitive evidence at this time that Reye's syndrome can generally be attributed to metabolic disorders. As discussed previously, other studies (Refs. 1, 2, and 3) have shown an association with aspirin ingestion and Reye's syndrome.

The agency notes one comment's statement that the incidence of Reye's syndrome is low despite many foods with naturally occurring salicylates. Salicylates occur in many foods at low concentrations and in certain foods at relatively high concentrations. For instance, a few herbs and spices contain as much as 200 milligrams salicylate per 100 grams (Ref. 10). However, these food products are generally consumed in small amounts. The agency has no information to suggest that salicylates in food are associated with Reye's syndrome. Although salicylates are present in a wide range of foods, the amount consumed from foods is generally lower than the therapeutic doses in drugs.

The references submitted by the comment that suggested that the acetylation mechanism of aspirin may be responsible for Reye's syndrome did not provide adequate information to support this suggestion. The references included discussion of the hydrolysis of acetylsalicylic acid into acetyl and salicylic acid moieties and the further hydrolysis of the acetyl moiety to acetate, which is ultimately metabolized to carbon dioxide. Up to 50 percent of orally administered doses of acetylsalicylic acid are hydrolyzed before they reach the blood stream because of esterases located in the gut wall and the clearance of the compound by the liver (Ref. 11). Packham (Ref. 12) noted that the acetyl moiety can rapidly acetylate cyclo-oxygenase in platelets at micromolar concentration. However, it may not remain in the circulation long enough to acetylate other proteins to an extent that alters their function. Salicylic acid is the circulating drug form which is shared by all salicylate products. It undergoes direct renal excretion and hepatic biotransformation through several enzymatic systems.

As noted in the October 1993 proposed rule (58 FR 54228 at 54229) there are some in vitro biochemical data that suggest salicylate may contribute to mitochondrial injury that is characteristic of Reye's syndrome. Based on a more recent in vitro study, Trost and Lemasters (Ref. 13) suggested that induction of the mitochondrial permeability transition (MPT) is a common pathophysiological mechanism causing mitochondrial injury in Reye's syndrome. In that study, MPT induction by aspirin required alkaline hydrolysis. Because aspirin spontaneously decomposes to salicylate, the authors said it is likely that salicylate, rather than acetylsalicylate, is the primary inducer of MPT.

While some in vitro studies (Refs. 14 and 15) suggest salicylate is responsible for mitochondrial injury that may be responsible for the pathogenesis of Reye's syndrome, the agency agrees with the comment that the evidence is not sufficient to show the salicylate moiety is responsible for Reye's syndrome. The pathogenesis of Reye's syndrome is not known. None of the submitted references link Reye's syndrome to either the salicylate or acetyl drug moiety.

Although the agency does not have definitive evidence that drugs containing nonaspirin salicylates significantly increase the risk of Reye's syndrome, a number of case reports (Ref. 8) suggest an association. Because of the serious consequences of Reye's syndrome, the agency has determined, in the interest of safe use of OTC drug 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 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.

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 licenced 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 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 (400) of the affected products are antidiarrheal drug products that contain bismuth subsalicylate as the active ingredient. The cost to implement the new Reye's syndrome warning for those products is significantly mitigated because the warning will be incorporated into the new labeling for those products as a result of publication of the final monograph for OTC antidiarrheal drug products.

The remaining 2 percent (100) of affected products includes OTC drug products containing aspirin and nonaspirin salicylates marketed under an NDA or ANDA or marketed under the tentative final monograph for OTC overindulgence drug products. A number of the overindulgence drug products that contain bismuth subsalicylate as the active ingredient also bear antidiarrheal claims and, thus, will need to be relabeled as a result of

publication of the final monograph for those drug products. The cost to add a warning to product labeling generally averages about \$2,000 to \$3,000 per SKU. Thus, the cost for these products to be relabeled is estimated to be between \$200,000 and \$300,000.

C. Small Business Impacts

Census data provide aggregate industry statistics on the total number of manufacturers for Standardized Industrial Classification Code 2384 Pharmaceutical Preparations by establishment size, but do not distinguish between manufacturers of prescription and OTC drug products. According to the U.S. Small Business Administration (SBA) designations for this industry, however, over 92 percent of the roughly 700 establishments and over 87 percent of the 650 firms are small. (Because census size categories do not correspond to the SBA designation of 750 employees, these figures are based on 500 employees.)

The agency's drug listing system indicates that between 900 and 1,500 marketers will need to relabel as the result of this final rule. Thus, the agency believes that many of the manufacturers affected by this final rule would be small. However, the cost of relabeling of private label products is incurred by the private label manufacturers, not the individual small marketers. The effect on individual firms will vary with the number of the firm's SKUs that require relabeling and the size and cost of the firm's labeling inventory. Most small firms will not incur significant regulatory costs because they manufacture few affected SKUs and use less expensive labeling stock. Because most firms will be able to incorporate these required changes when incorporating other regulatory requirements, this final rule should have a minimal economic impact on small entities.

D. Alternatives

The agency considered and rejected a more costly alternative that would have required all products to be relabeled within 12 to 18 months of publication of this final rule in the **Federal Register**, with a multimillion dollar cost to industry based on the potential number of affected products. Because 80 percent of the products (a number of which have multiple SKUs) already have a Reye's syndrome warning on their label, the agency concluded that the incremental benefits of a reworded warning did not outweigh the costs. As discussed in section II, comment 11 of this document, the agency has set the implementation date of this final rule for the Reye's syndrome warning for OTC antidiarrheal drug products that contain bismuth subsalicylate as an active ingredient to coincide with the compliance dates for the final monograph for those drug products. The agency considers this a reasonable time for manufacturers to implement these final rules, and the costs associated with implementation will be less for one label change than for two label changes. The agency has also set the compliance dates for the majority of the products (internal analgesic, antipyretic, and antirheumatic) affected by this final rule to coincide with the final monograph for those drug products, to be published in the future. The agency encourages manufacturers to relabel their products voluntarily, if new labeling is implemented before that final monograph publishes.

The agency considered, but rejected, an exemption from coverage for small entities because the new labeling information is also needed by consumers who purchase products marketed by those entities. However, longer compliance dates are being provided for antidiarrheal and overindulgence drug products containing bismuth subsalicylate with annual sales less than \$25,000 (an

additional 12 months) and for products containing aspirin and nonaspirin salicylates marketed under an NDA or ANDA (an additional 6 months).

E. Conclusion

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.

This analysis shows that the agency has considered the burden to small entities and provided compliance dates that should significantly reduce the burden. Thus, the agency certifies that this final rule will not have a significant impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

FDA concludes that the warning statement set forth in this final rule is not subject to review by the Office of Management and Budget because it does not constitute a “collection of information” under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the required labeling is a “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. References

The following references are on display in the Dockets Management Branch (see section I of this document) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Halpin, T. et al., "Reye's Syndrome and Medication Use," *Journal of the American Medical Association*, 248:687–723, 1982.
2. Hurwitz, E. et al., "Public Health Service Study of Reye's Syndrome and Medications: Report of the Pilot Study," *New England Journal of Medicine*, 313:849–857, 1985.
3. Hurwitz, E. et al., "Public Health Service Study of Reye's Syndrome and Medications: Report of the Main Study," *Journal of the American Medical Association*, 257:1905–1911, 1987.
4. Forsyth, B. et al., "New Epidemiologic Evidence Confirming that Bias Does Not Explain the Aspirin/Reye's Syndrome Association," *Journal of the American Medical Association*, 261:2517–2524, 1989.
5. Orlowski, J. et al., "A Catch in the Reye," *Pediatrics*, 80:638–642, 1987.

6. Orłowski, J. et al., "Reye's Syndrome: A Case Control Study of Medication Use and Associated Viruses in Australia," *Cleveland Clinic Journal of Medicine*, 57:323–329, 1990.
7. Biometric Research Institute, "Analysis of Exposure to Non-Aspirin Salicylates Among Subjects from the Ohio Department of Health Survey and the Public Health Service Pilot Study on Reye Syndrome," June 13, 1986, in comment C2, Docket No. 93N–0182, Dockets Management Branch.
8. Adverse Drug Reaction Reports, in OTC Vol. 03RSFR, Docket No. 93N–0182, Dockets Management Branch.
9. Orłowski, J. P., "Whatever Happened to Reye's Syndrome? Did It Ever Really Exist?" *Critical Care Medicine*, 27:1582–1587, 1999.
10. Swain, A., "Salicylates in Foods," *Journal of the American Dietetic Association*, 85:950–960, 1985.
11. Reigelman, S., "The Kinetic Disposition of Aspirin in Humans," in *Aspirin, Platelets, and Stroke* (Chapter X), edited by W. S. Fields and W. K. Hess, W. H. Green Inc., St. Louis, MO, pp. 105–114, 1971.
12. Packham, M., "Mode of Action of Acetylsalicylic Acid," in *Acetylsalicylic Acid: New Uses for an Old Drug*, edited by H. Barnett et al., Raven Press, New York, NY, pp. 63–82, 1982.
13. Trost, L. C., and J. J. Lemasters, "The Mitochondrial Permeability Transition: A New Pathophysiological Mechanism for Reye's Syndrome and Toxic Liver Injury," *The Journal of Pharmacology and Therapeutics*, 278:1000–1005, 1996.
14. Martens, M. E., and C. Lee, "Reye's Syndrome: Salicylates and Mitochondrial Functions," *Biochemical Pharmacology*, 33:2869–2876, 1984.
15. Yoshida, Y. et al., "Effect of Salicylic Acid on Mitochondrial Peroxisomal Fatty Acid Catabolism," *Pediatric Research*, 23:338–341, 1988.

16. National Institutes of Health, Consensus Conference, "Diagnosis and Treatment of Reye's Syndrome," *Journal of the American Medical Association*, 246:2441–2444, 1981.

17. Wolinsky, J. S., "Reye's Syndrome," in *Cecil Textbook of Medicine*, 19th ed., edited by J. B. Wyngaarden et al., W. B. Saunders Co., Philadelphia, PA, pp. 2194–2195, 1992.

18. Adverse Drug Reaction Reports, in OTC Vol. 03RSNPR, Docket No. 93N–0182, Dockets Management Branch.

19. Betts, R., "Influenza," in *Principles and Practices of Infectious Diseases*, 4th ed., edited by G. L. Mandell, J. E. Bennett, and R. Dolin, Churchill Livingstone, New York, NY, pp. 1546–1567, 1995.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.314 is amended by revising paragraphs (h)(1) and (h)(4) to read as follows:

§ 201.314 Labeling of drug preparations containing salicylates.

* * * * *

(h)(1) The labeling of orally or rectally administered over-the-counter drug products containing aspirin or nonaspirin salicylates as active ingredients subject to this paragraph is required to prominently bear the following warning: “Reye’s syndrome [subheading in bold type]: Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye’s syndrome, a rare but serious illness.”

* * * * *

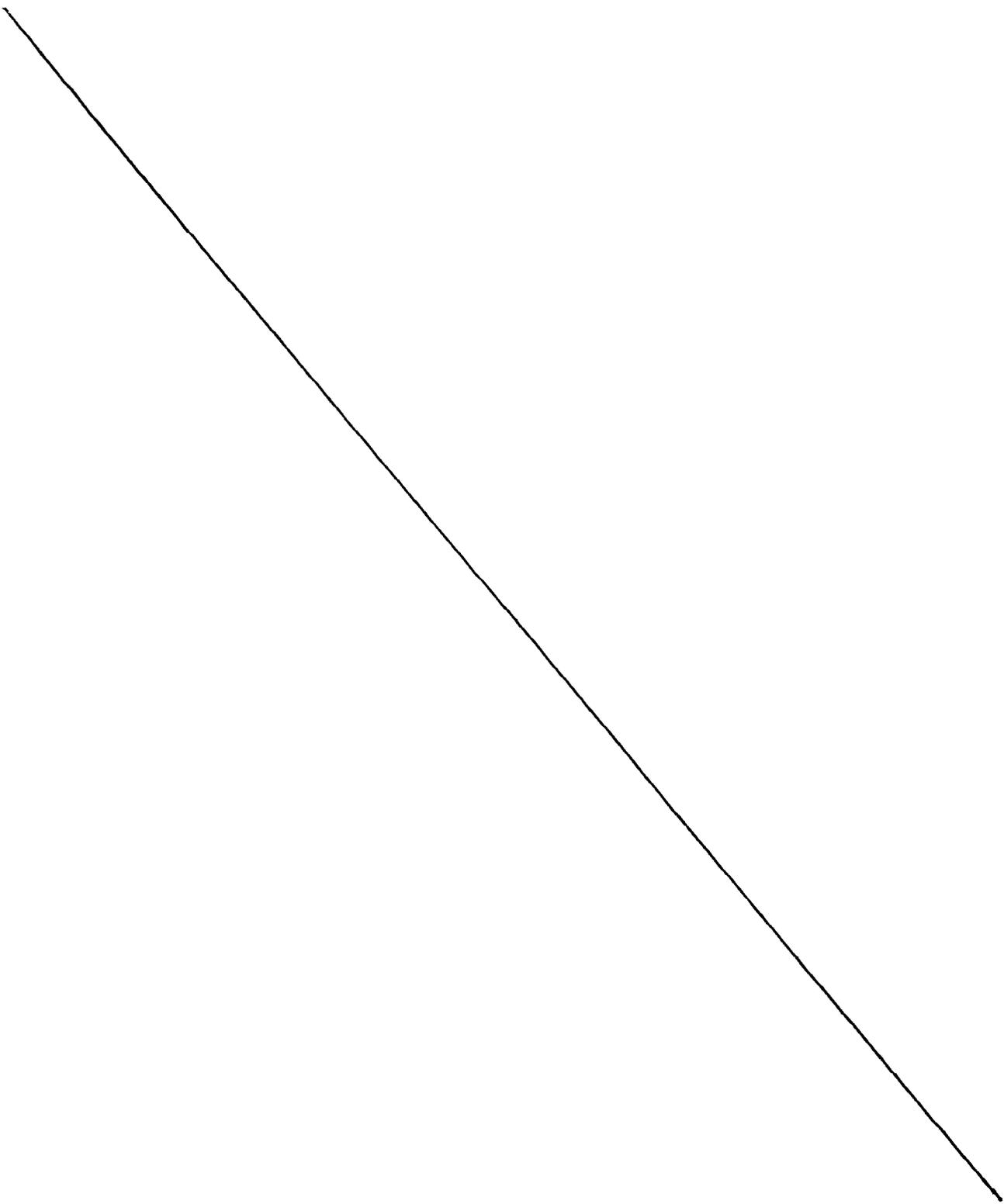
(4) Any product subject to paragraphs (h)(1), (h)(2), and (h)(3) of this section that is not labeled as required by these paragraphs and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(i) Compliance by [*insert date 18 months after date of publication in the Federal Register*], for OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under a new drug application or abbreviated new drug application.

(ii) Compliance by [*insert date 12 months after date of publication in the Federal Register*], for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales greater than \$25,000.

(iii) Compliance by [*insert date 24 months after date of publication in the Federal Register*], for OTC antidiarrheal and overindulgence drug products that contain bismuth subsalicylate as an active ingredient and have annual sales less than \$25,000.

(iv) Compliance dates for all other OTC drug products containing aspirin and nonaspirin salicylates as an active ingredient and marketed under an OTC drug monograph (for internal analgesic, antipyretic, and antirheumatic drug products, or for menstrual drug products) will be established when the final monographs for those products are published in a future issue of the **Federal**



Register. In the interim, these products should continue to be labeled with the previous Reye's syndrome warning that appears in paragraph (h)(1) of this section.

Dated: 3/31/03

March 31, 2003.



Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 03-????? Filed ??-??-03; 8:45 am]

BILLING CODE 4160-01-S

TO BE KEPT
COPY OF THE ORIGINAL
