DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 93N-0182]

RIN 0905-AA06

Labeling of Oral and Rectal Over-The-Counter Drug Products Containing Aspirin and Nonaspirin Salicylates; Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise the Reye syndrome warning required for oral and rectal over-the-counter (OTC) human drug products containing aspirin. FDA is also proposing to require the warning on OTC drug products containing nonaspirin salicylates. The revised warning will inform consumers of the initial symptoms of Reye syndrome and advise that aspirin or nonaspirin salicylate products should not be given to children or teenagers who are recovering from chicken pox or the flu. FDA is issuing this proposal after considering comments submitted to the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products and other available information.

DATES: Written comments by December 20, 1993. Written comments on the agency's economic impact determination by December 20, 1993. FDA is proposing that the final rule based on this proposal be effective 6 months after the date of publication of the final rule in the **Federal Register**.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

SUPPLEMENTARY INFORMATION:

I. Introduction

Reye syndrome is a rare but serious illness that affects young people. The agency has received reports associating Reye syndrome with the use of aspirin and nonaspirin salicylate drug products. In the **Federal Register** of March 7, 1986 (51 FR 8180), FDA published a final regulation requiring that the labeling of oral and rectal OTC aspirin and aspirin-containing drug products include a warning that these drug products should not be used to treat chicken pox or flu symptoms in children and teenagers before consulting a doctor about Reye syndrome. The warning appears in § 201.314(h) (21 CFR 201.314(h)). The regulation provided that the Reye syndrome warning requirement would expire June 6, 1988, unless the agency acted to extend it. In the **Federal Register** of January 22, 1988 (53 FR 1796), FDA proposed to make permanent the requirement for a Reye syndrome warning, and in the **Federal Register** of June 9, 1988 (53 FR 21633), FDA made the warning permanent for oral and rectal OTC drug products containing aspirin.

In the **Federal Register** of November 16, 1988 (53 FR 46204), FDA published a notice of proposed rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products. The agency indicated (53 FR 46204 at 46205) that the Reye syndrome warning finalized in the **Federal Register** of June 9, 1988, would be incorporated into the final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products. Interested persons were invited to file by May 16, 1989, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. New data could have been submitted until November 16, 1989, and comments on the new data could have been submitted until January 16, 1990.

The National Reye's Syndrome Foundation (NRSF) commented that the Reye syndrome warning currently required for OTC aspirin and aspirin-containing drug products should be extended to all salicylate-containing drug products (Ref. 1). NRSF did not include any data to support its request, but stated that too many cases of Reye syndrome have been linked to one product, not intended for use as an analgesic, that contains bismuth subsalicylate, for this to be a coincidental occurrence.

Subsequently, the agency became aware that a manufacturer of a widely marketed OTC drug product containing bismuth subsalicylate (used for the relief of symptoms associated with overindulgence in food and drink) had voluntarily included a Reye syndrome warning in the product's labeling (Ref. 2). The warning is similar to the warning required by § 201.314(h)(1). In a proposed amendment to the tentative final monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink, published in the **Federal Register** of May 5, 1993 (58 FR 26886), the agency proposed a Reye syndrome warning for OTC overindulgence drug products that contain bismuth subsalicylate. That warning states: "WARNING: 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 also stated that it was considering the appropriateness of revising the current Reye syndrome warning for oral and rectal OTC drug products containing aspirin in § 201.314(h)(1) to be similar to the language in the May 5, 1993, proposal. The agency stated that based on the comments received, in a future issue of the **Federal Register**, the agency may propose to revise the current Reye syndrome warning in § 201.314(h)(1). The comment period for that proposal closed on July 6, 1993. The agency received four comments in response to the proposal. The agency is currently evaluating the comments that were received. Before a final decision is made, the agency finds it appropriate, at this time, to propose revising the current Reye syndrome warning and also extending it to nonaspirin salicylates. The agency will evaluate all comments on both proposals before making a final decision.

At the time that FDA promulgated the existing Reye syndrome warning for OTC drug products containing aspirin, scientific research was focused primarily on the association of Reye syndrome and aspirin rather than the broader category of drug products containing nonaspirin salicylates. Thus, the warning was limited to aspirin.

In the final rule for the labeling of oral and rectal OTC aspirin and aspirin-containing drug products (53 FR 21633 at 21635), the agency noted that a Public Health Service study (Ref. 3) reported that there were too few subjects whose reported exposures were to nonaspirin salicylates for a meaningful analysis. Almost all of the case subjects and the majority of the controls who took salicylates took aspirin; only a small percentage of subjects took nonaspirin salicylates. Only 1 case subject and 11 controls were exposed to bismuth subsalicylate, and only 2 controls were exposed to magnesium salicylate. In assessing the independent risk of aspirin and nonaspirin salicylates, a significant association was found with

aspirin. However, the authors reported that the risk associated with nonaspirin salicylates independent of aspirin could not be assessed because only two case subjects did not have a confounding exposure to aspirin. In the final rule, the agency stated its belief that, at the time, priority must be given to continuing the warning on OTC aspirin and aspirin-containing drug products. Further, the agency indicated that it would consider extending the scope of the warning to nonaspirin salicylates if warranted by further research or other appropriate information (53 FR 21633 at 21635).

II. The Agency's Proposal

While cases of Reye syndrome are rare, the agency is aware of two fatalities from Reye syndrome—one reported to be associated with the use of bismuth subsalicylate and the other associated with the use of a calcium salicylate containing drug product (Ref. 4). One death, which occurred in January 1989, involved a 6-year-old child who reportedly developed Reye syndrome following the administration of the label-recommended dosage of an OTC bismuth subsalicylate product for the treatment of flu-like symptoms, diarrhea, and nausea. The other death, which occurred in 1985, involved a 3-month-old infant whose upper respiratory tract infection was treated with a theophylline drug product that included calcium salicylate as a solubilizing agent. Sarrll and Duxbury (Ref. 5) reported one case of Reye syndrome associated with the use of teething gel containing choline salicylate. No outcome was mentioned. In addition, animal and in vitro biochemical data suggest that salicylic acid/salicylate may contribute to the metabolic derangement of liver cell mitochondria that leads to the mitochondrial injury characteristic of Reye syndrome (Refs. 6 through 9).

Aspirin is deacetylated in the gut, blood, and liver to salicylic acid, and the major plasma component after ingestion of aspirin is salicylate, the ionized form of salicylic acid (Ref. 10). Because the exact role of aspirin and its metabolic products in Reye syndrome is unknown, the agency believes the aspirin association with Reye syndrome may be applicable to nonaspirin salicylate products as well. Some manufacturers of OTC and prescription drug products containing nonaspirin salicylates currently voluntarily include a warning against the use of these drug products in children and teenagers for flu or chicken pox symptoms (Refs. 11 and 12). Accordingly, the agency is proposing that OTC internal analgesic/antipyretic drug products containing any nonaspirin salicylates bear a Reye syndrome warning. The tentative final monograph identified the following ingredients as nonaspirin salicylates: Calcium salicylate, magnesium salicylate, potassium salicylate, and sodium salicylate (53 FR 46204 at 46249).

In the amendment to the tentative final monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink (58 FR 26886 at 26888), the agency proposed the following Reye syndrome warning for products that contain bismuth subsalicylate: "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." This proposed warning differs from the existing warning in § 201.314(h)(1), which states: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness reported to be associated with aspirin." However, as discussed in the proposal for bismuth subsalicylate products, the agency believes that the new warning provides important additional information (i.e., not to use such products during the period when the child appears to be recovering from the flu or chicken pox, plus a description of the earliest recognizable symptoms of Reye syndrome) that should be included in the labeling of these OTC drug products. The agency considers the more specific information provided by the proposed warning particularly important now that public education programs on Reye Syndrome have significantly diminished. Further, the agency believes that all salicylate containing OTC drug products should bear uniform labeling with respect to Reye syndrome. While the existing warning has served its purpose well, the agency considers the newer warning being proposed to be more informative to future users of these products. Therefore, the agency is proposing that all OTC drug products containing aspirin or nonaspirin salicylates (including bismuth subsalicylate) bear the newer proposed warning.

FDA is proposing to amend § 201.314(h) now, instead of proposing to include the warning in the final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products when that monograph is issued at a future date. This approach will bring uniformity and consistency to the labeling of OTC drug products containing aspirin or nonaspirin salicylates, at the earliest possible date. When the final monograph is issued, it will contain a cross-reference to the Reye syndrome warning in § 201.314(h). That warning will apply to all OTC aspirin and nonaspirin salicylates whether or not marketed pursuant to an OTC drug monograph. The agency invites comment on the newly proposed Reye syndrome warning.

References

(1) Comment No. C144, Docket No. 77N-0094, Dockets Management Branch.

(2) Copy of Labeling for Pepto-Bismol, in OTC Vol. 03RSNPR, Docket No. 93N-0182, Dockets Management Branch.

(3) Hurwitz, E. S. et al., "Public Health Service Study of Reye's Syndrome and Medications," *Journal of the American Medical Association*, 257(14):1905–1911, 1987.

(4) Adverse Drug Reaction Reports, in OTC Vol. 03RSNPR, Docket No. 93N-0182, Dockets Management Branch.

(5) Sarrll, D. W. and A. J. Duxbury, "Choline Salicylates and Reye Syndrome," *British Dental Journal*, 9:317–318, 1986.

(6) Pranzatelli, M. R. and D. C. De Vivo, "Review Pharmacology of Reye Syndrome," *Clinical Neuropharmacology*, 10:96–125, 1987.

(7) Trauner, D. A., E. Horvath, and L. E. Davis, "Inhibition of Fatty Acid Beta Oxidation by Influenza B Virus and Salicylic Acid in Mice: Implications for Reye's Syndrome," *Neurology*, 38:239–241, 1988.

(8) Martens, M. E. and C. Lee, "Reye Syndrome: Salicylates and Mitochondrial Functions," *Biochemical Pharmacology*, 33:2869–2876, 1984.

(9) Yoshida, Y. et al., "Effect of Salicylic Acid on Mitochondrial Peroxisomal Fatty Acid Catabolism," *Pediatric Research*, 23:338–341, 1988.

(10) Shearn, M. A., "Nonsteroidal Anti-inflammatory Agents; Nonopiate Analgesics; Drugs Used in Gout," in "Basic and Clinical Pharmacology," 2d ed., edited by B. G. Katzung, Lange Medical Publications, Los Altos, CA, pp. 400–403, 1984.

(11) Schumacher, M. M., editor, "Physicians Desk Reference for Nonprescription Drugs," 13th ed., Medical Economics Co., Inc., Montvale, NJ, pp. 549–550, 1992.

(12) Schumacher, M. M., editor, "Physicians Desk Reference for Prescription Drugs," 47th ed., Medical Economics Co., Inc., Montvale, NJ, pp. 1891–1892, 1993.

III. Economic Impact

FDA has examined the regulatory impact and regulatory flexibility implications of this proposed rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). This proposed regulation imposes direct one time costs associated with changing product labels to include the required labeling statement. FDA

'mates those costs to total less than nillion. Therefore, the agency has ..etermined that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined by the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC oral and rectal drug products containing aspirin or nonaspirin salicylates. Types of impact may include but are not limited to costs associated with relabeling or repackaging.

Comments regarding the impact of this rulemaking on OTC drug products containing aspirin or nonaspirin salicylates should be accompanied by appropriate documentation. A period of 60 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the reamble to the final rule.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) 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.

Interested persons may, on or before December 20, 1993, submit written comments on the proposed regulation to the Dockets Management Branch (address above). Written comments on the agency's economic impact determination may be submitted on or before December 20, 1993. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

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, it is proposed that 21 CFR part 201 be amended as follows:

PART 201—LABELING

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 376); secs. 215, 301, 351, 361 of the Public Health Service Act (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 subject to this paragraph is required to prominently bear the following warning: "WARNING: 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."

* * * * *

(4) Any product subject to this paragraph that is not labeled as required by this paragraph and that is initially introduced or initially delivered for introduction into interstate commerce after [insert date 6 months after date of publication of the final rule in the Federal Register], is misbranded under sections 201(n) and 502 (a) and (f) of the Federal Food, Drug, and Cosmetic Act.

Dated: August 17, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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