DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 85N-0553]

Labeling for Oral and Rectal Over-the-Counter Aspirin and Aspirin-Containing Drug Products

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to require that the labeling of oral and rectal over-the-counter (OTC) aspirin and aspirin-containing drug products for human use bear a warning that such products should not be used to treat chicken pox or flu symptoms in children and teenagers before consulting a doctor about Reye syndrome, a rare but serious illness. FDA is taking this action in order to bring uniformity and consistency to the marketplace and to aid in increasing the public awareness about this disease.

DATES: These final regulations are effective June 5, 1986.

FOR FURTHER INFORMATION CONTACT: Christopher Smith, Office of the Commissioner (HF-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5133.

SUPPLEMENTARY INFORMATION:

Background

In the Federal Register of December 17, 1985 (50 FR 51401), FDA proposed to require that the labeling of oral OTC aspirin and aspirin-containing drug products for human use bear a warning that such products should not be used to treat chicken pox or flu symptoms in children and teenagers before consulting a doctor about Reye syndrome, a rare but serious illness. FDA proposed this rule in order to bring uniformity and consistency to the marketplace and to aid in increasing the public awareness about this disease.

In the proposal, FDA described: (a) Reye syndrome and its symptoms; (b) the early scientific studies that were conducted to look at the possible association between the use of aspirin and the onset of Reye syndrome; (c) the Public Health Service (PHS) study now being conducted under the direction of the PHS Reye Syndrome Task Force; and (d) the educational activities that have been carried out by FDA and aspirin industry about the use of aspirin and Reye syndrome. FDA acknowledged in the proposal and the successful voluntary public education and labeling efforts made by the aspirin industry, but noted that these voluntary efforts led to considerable diversity in the specific message being conveyed to consumers, particularly through product labeling. A complete discussion of this diversity along with examples of product labeling and the concerns expressed by several organizations are contained in the proposed rule.

FDA also noted that, under the voluntary program, it was unable to ascertain with certainty whether all aspirin-containing products that should be labeled with the warning statement have, in fact, been labeled.

II. Highlights of the Final Rule

As described further below, all the comments received on the proposal expressed support for the new regulation. Thus, to increase consumer awareness, to avoid public confusion, and to achieve uniformity in the marketplace, FDA is issuing a final regulation which closely parallels the proposal.

As in the proposal, the final rule requires the following labeling statement:

"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."

Also like the proposal, FDA is requiring that this warning precede any additional warnings that may appear on the product labeling in order to assure the prominence of the message.

In addition, in response to comments received on the proposal (described below), FDA is adding rectal OTC aspirin and aspirin-containing products within the scope of this regulatory action, and is making it clear that this final rule preempts State and local labeling requirements that are not identical to it with respect to oral and rectal OTC aspirin and aspirin-containing drug products for human use. The final rule and this preamble also contain some minor clarifications to statements in the proposal or to comments received.

III. Comments

FDA received 17 comments on the proposed rule: 4 from industry, 6 from trade associations, 3 from health professional associations, 2 from State agencies, 1 from a consumer group, and one from FDA staff. All comments were positive and expressed support for the agency's action. Some suggested changes in the proposal or expressed concerns with specific portions of the proposal.

A. Individual Manufacturer's Comments

FDA received comments from four pharmaceutical firms. Two expressed concern that since they had participated in the voluntary program and were labeling their products with a warning statement, they should be allowed to use up existing supplies of labels now in inventory, or that, at a minimum, FDA should extend the effective date in order to allow for most such inventories to be used. Two other firms suggested that their present labeling contains warning statements that, although not exactly as that proposed by FDA, are close enough in their language to be acceptable.

FDA disagrees that stocks of labels that are in inventory or labeling that is not exactly like that in the final rule, but close to that in the final rule, should be allowed to be used as a matter of course. While FDA recognizes that some firms may be inconvenienced after having already changed their labels in order to participate in the voluntary program, the purpose of this rule is specifically to bring uniformity and consistency to the marketplace. However, FDA points out that the new regulatory requirement is directed to the initial introduction of the product into interstate commerce. Thus, products in retail packaging that are labeled with an earlier Reye syndrome warning, and that have been initially introduced into interstate commerce prior to the effective date of this rule, will be permitted to be sold. In contrast, products produced in retail packaging, and initially delivered for introduction into interstate commerce on or after the effective date of this rule, will be required to be in compliance with the new requirements.

FDA also is not extending the rule's effective date. This is to help ensure that aspirin and aspirin-containing products that are on the store shelves by the next flu season will be labeled according to this final rule. FDA recognizes that there may be a few small manufacturers for whom, for various financial or other reasons, it is impossible to comply with this final rule by the effective date. In these unusual circumstances, FDA will consider requests for limited extensions. Such requests should be sent to Office of Compliance, Center for Drugs and Biologics, HFN-300, Food and Drug Administration, 5600 Fishers Lane,

Rockville, Maryland 20857, and should document both the need for an extension and the duration of time requested.

B. Comments From Trade Associations

FDA received comments from six trade associations. While none of the industry trade associations that commented suggested a delay in the effective date for the rule, or a time period during which labels printed with the voluntary warning should still be allowed, several of the comments did request that FDA allow for the "sell-through" of current stocks already in the distribution chain. FDA agrees with these comments and, as discussed earlier, will allow the "sell-through" of products already in interstate commerce.

Comments also were received expressing concern that the proposal was unclear about the exact type of product material on which the warning statement must appear. In response to the comments, the final rule has been clarified to state that the warning statement must appear in several places. First, the warning is required to appear on the label of the immediate container. Second, in cases where the immediate container is not the retail package (e.g., where a bottle of tablets is packaged in a box), the retail package must also bear the warning statement. Finally, the warning statement must appear on any labeling that contains other warnings, and, in such cases, the Reye warning is required to be the first warning under the heading "Warnings." However, items such as "shelf talkers," store displays or money-saving coupons would not be required to bear the warning statement.

Two trade association comments suggested that FDA preempt State requirements for label warnings regarding Reye syndrome. While FDA is unaware of any such requirements at this time, FDA agrees with the comments. FDA is authorized to assure the safety of drugs marketed in interstate commerce in this country. The manufacturing and distribution system for these products is national in scope and the measures adopted by FDA to regulate this national system should be adequate to safeguard the interests of the entire population. While State and local requirements for products may on occasion be appropriate and necessary, such measures should not interfere with FDA's accomplishing those purposes that are within its Congressionally mandated area of responsibility. State and local requirements for the labeling of oral and rectal OTC aspirin-containing drug products that differ from those established by this final rule would interfere with the accomplishment of FDA's objective to bring consistency and uniformity to the marketplace with respect to the labeling of these products regarding Reye syndrome. Thus, FDA intends that the regulations issued in this document preempt State and local packaging requirements that are not identical to it with respect to oral and rectal OTC aspirin-containing drug products for human use.

C. Comments From Health Professional Associations

FDA received comments from three health professional associations. Two comments urged that the warning include more explicit language about aspirin and Reye syndrome such as "Studies show that aspirin may increase the risk of developing Reye syndrome." While FDA has stated that the available data do not establish a definitive cause-and-effect relationship between aspirin-containing products and the disease, the agency has concluded that the studies that have been done to date suggest a possible association between aspirin use and Reye syndrome. Thus, FDA felt it was appropriate to carry out a public awareness campaign and to encourage voluntary industry public education efforts. However, in the proposal FDA specifically states that the impetus for the rule is to bring consistency and uniformity to the marketplace with respect to the warning statement. For these reasons, FDA believes that the warning statement as proposed is sufficient at this time and the agency disagrees with the comment. The final rule is, however, an interim measure in that it will expire in 2 years. FDA will consider the need for a change in the warning statement based upon the available data at that time.

One comment suggested that the final rule be extended to cover aspirin-containing prescription drug products as well as those available OTC. FDA does not agree at this time that this final rule should be applied to prescription drugs. The warning statement required by the rule is aimed at consumers buying and using aspirin-containing products without the advice of a physician. Thus, the statement required by the final rule suggests that persons consult a doctor before using the drug in certain circumstances. Prescription drugs are dispensed only on the order of a physician. FDA informs physicians of such matters as the possible association between aspirin and Reye syndrome in many ways including information bulletins and requirements under the prescription drug regulations. Therefore, FDA believes it is taking the appropriate action with regard to Reye syndrome and OTC drugs at this time. However, in 2 years, upon expiration of this final rule, if the agency seeks to continue the requirement based upon new information available then, the agency may reconsider the need for a warning in the professional labeling for prescription drug products.

Finally, one health professional group suggested that the required warning statement include pharmacists as a group that might be consulted prior to the use of the medication. FDA disagrees with this comment because the warning statement suggests that consultation be obtained about a disease, Reye syndrome, rather than information about a pharmaceutical product.

D. State Comments

FDA received comments from two State organizations. One comment simply expressed support for the proposal. The other, while advocating the labeling requirement, suggested that the warning also require a listing of the symptoms of Reye syndrome. FDA agrees that the public should be knowledgeable of the symptoms of Reye syndrome, and both FDA and the aspirin industry have included that information as part of the public education campaign described in the proposal. However, the purpose of the label warning is preventive—i.e., that aspirin should not be used for certain purposes without first consulting a physician. Thus, including the symptoms of Reye syndrome on the product label would not further that purpose.

E. Consumer Group Comments

FDA received comment from one consumer organization. While supportive of the agency's efforts to require a warning, the group did offer several suggested changes. The comment supported the proposal and called for the effective date to be May 30, 1986, even if the time period between publication and the effective date needed to be shortened from 90 days. FDA disagrees. The effective date of this regulation is June 5, 1986, which is not appreciably different from the proposed effective date of May 30, 1986.

The comment also suggested that the warning statement be required to be boxed so that it will be highlighted to the consumer. FDA does not believe a boxed warning is necessary. The requirement that the warning be the first warning under the heading "Warning" appropriately highlights the information.

Another part of the comment suggested that the warning include the statement that Reye syndrome is "often fatal." While FDA agrees that Reye syndrome can be fatal, in the majority of cases it is not. FDA therefore believes the warning, as proposed, is appropriate, and that the consumer's physician can discuss such specifics as the disease's fatality rate as the need arises.

The comment also suggested that products subject to this rule that are indicated for use by both children and adults be required to have in the "Indications" section a clarification that the product should not be used by persons under 21 for the treatment of flu or chicken pox or, at a minimum, that the "Indications" section should contain a cross-reference to the Reye syndrome warning elsewhere in the labeling. FDA does not agree that an additional statement should be required in the "Indications" section or that a cross-reference is needed. FDA believes that the placement of the required warning statement as the first warning under the "Warning" section is an appropriate method of conveying the information to teenagers who may use adult aspirin products and to those who may consider the use of these products to treat children with flu or chicken pox.

Finally, the comment urged that FDA extend the labeling requirements to prescription drugs. FDA disagrees with this suggestion for reasons already discussed.

F. FDA Staff

One comment was filed by employees of the agency's Center for Drugs and Biologics who suggested that the rule be extended to include aspirin and aspirin-containing OTC rectal suppository drugs. The comment pointed out that such products are often used in patients unable to take oral medication, especially in infants, or when oral medication is not retained. The comment also noted that comparison of absorption of rectal versus oral doses of aspirin show that the rectal absorption can be equivalent to that obtained by the oral dose. FDA agrees with the comment and is including rectal OTC aspirin and aspirin-containing drug products in the final rule.

IV. Agency Action

FDA has evaluated the comments as well as information already in the agency's files and concludes that, for the reasons stated above, the proposed labeling for oral and rectal OTC aspirin and aspirin-containing drug products is necessary and appropriate and that the regulations should be amended as set forth below.

The agency laid out its legal authority and assessed the economic and environmental impact of this rule in the proposal of December 17, 1985 (50 FR 51401). This assessment concluded that the proposed rule was not a major rule as defined by Executive Order 12291. No new information or comments were received that would alter this determination or the agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

List of Subjects in 21 CFR Part 201

Drugs, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act, Part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR Part 201 is revised to read as follows:

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1056 as amended (21 U.S.C. 321, 352, 355, 371); 21 CFR 5.10 and 5.11.

2. In § 201.314 by adding new paragraph (h) to read as follows:

§ 201.314 Labeling of preparations containing salicylates.

* * * * *

(h)(1) The labeling of orally or rectally administered over-the-counter aspirin and aspirin-containing drug products subject to this paragraph is required to prominently bear a warning. The warning shall be as follows: "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."

(2) This warning statement shall appear on the immediate container labeling. In cases where the immediate container is not the retail package, the retail package also must bear the warning statement. In addition, the warning statement shall appear on any labeling that contains warnings and, in such cases, the warning statement shall be the first warning statement under the heading "Warnings."

(3) Over-the-counter drug products subject to this paragraph and labeled solely for use by children (pediatric products) shall not recommend the product for use in treating flu or chicken pox.

(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 June 5, 1986, is misbranded under sections 201(n) and 502 (a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(5) The requirements of this paragraph shall expire June 6, 1988 unless extended by the Food and Drug Administration by publication for notice and comment in the Federal Register.

Dated: February 27, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

Otis R. Bowen, M.D.,

Secretary of Health and Human Services.

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