[4110-03]

[Docket No. 78N-0263]

ANTACID DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Final Classification of Category III Antacid Ingredients and Labeling Claims

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This document contains the final decision that over-the-counter (OTC) antacid drug products having certain ingredients or combinations of ingredients and having certain labeling claims would be considered not generally recognized as safe and effective for their intended use or, in the case of labeling, would be misbranded (Category II). OTC antacid drug products with the conditions subject to this notice are therefore regarded as new drugs requiring approved new drug applications before they can be marketed in interstate commerce.

EFFECTIVE DATE: March 5, 1979.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs issued in the FEDERAL REGISTER of June 4, 1974 (39 FR 19862) the final order for OTC antacid drug products generally recognized as safe and effective and not misbranded (21 CFR part 331). This order was issued under the OTC drug review procedures (21 CFR 330.10) promulgated in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464) and the conclusions and recommendations of the Advisory Review Panel on OTC Antacid Drug Products.

Section 330.10(a)(5) of the OTC drug review procedures defines Category I, Category II, and Category III conditions as follows:

(i) A recommended monograph or monographs covering the category of OTC drugs and establishing conditions under which the drugs involved are generally recognized as safe and effective and not misbranded (Category I). This monograph may include any conditions relating to active ingredients, labeling indications, warnings and adequate directions for use, prescription of OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph.

(ii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding (Category II).

(iii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that the available data are insufficient to classify such condition under either paragraph (a)(5) (i) or (ii) of this section and for which further testing is therefore required (Category III). The report may recommend the type of further testing required and the time period within which it might reasonably be concluded.

In the FEDERAL REGISTER of April 12, 1977 (42 FR 19137), the Commissioner amended § 330.10(a) to permit any product with a Category III condition (e.g., ingredient, combination of ingredients, labeling claim) to remain on the market or be introduced into the market during the testing period if the Food and Drug Administration (FDA) receives notification, pursuant to 21 CFR 330.10(a)(13), that the number of studies specified in the applicable testing guidelines will be undertaken to obtain the data necessary to resolve the issue that resulted in Category III classification. Under § 330.10(a)(13)(v), FDA must issue a notice in the FEDERAL REGISTER, as soon as possible after the date for submitting a Category III notification statement, listing each Category III condition for which notification statements have been filed. The notice must also list each Category III condition for which notification statements have not been received and place these conditions in Category II, indicating the date when products containing such conditions may no longer by shipped in interstate commerce. The revised Category III testing regulations thus permit the Commissioner to remove from the marketplace products that have no potential for reaching Category I prior to the expiration of the time allotted for Category III testing.

At the time of publication of the final order for OTC antacid drug products, however, the regulations did not require a sponsor to submit a notice of intent to test a Category III condition. The June 4, 1974, order provided a testing period until June 5, 1976. Accordingly, until the expiration of the time allowed, the Commissioner could not make a final determination of the status of any Category III condition, irrespective of whether it was the subject of testing.

Moreover, although the 2-year Category III testing period established by the final order for OTC antacid drug products expired on June 5, 1976, reclassification of the conditions for which no studies had been performed was further delayed in the expectation that the test results on those Category III conditions that had been studied, and for which petitions to amend the monograph had been received, could be quickly evaluated and the status of all Category III conditions announced at one time.

During the Category III testing period provided for OTC antacid drug products, data were submitted to FDA by Marion Laboratories, Inc., in support of a foam-forming floating antacid combination product containing the ingredients aluminum hydroxide dried gel, magnesium trisilicate, alginic acid, and sodium bicarbonate (OTC File No. 31-00088). In addition, two firms submitted data to support amendment of part 331 (the antacid monograph) to include the labeling indication "upset stomach" (Miles Laboratories, Inc. (OTC file No. 31-000192) and Warner-Lambert Co. (OTC file No. 31-11370)).

Review of the petitions to amend the antacid monograph has been complicated by several factors. The claim "upset stomach due to overindulgence in food and drink" is currently under review by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. Although this claim is different from the "upset stomach" claim for which supporting data were submitted in the two petitions to amend the antacid monograph, the Commissioner has determined that it is appropriate to coordinate certain aspects of the review of these petitions with the ongoing review by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. Accordingly, the final evaluation of the petitions to amend the antacid monograph to include the claim of "upset stomach" has been delayed.

In the case of the petition to amend the monograph to include an antacid combination containing alginic acid in Category I, the petitioner has clarified the rationale for including alginic acid in its final formulation, i.e., alginic acid reacts with the sodium bicarbonate in the formulation to form a foam that carries the antacid ingredients and floats on the stomach contents. The petitoner calls this a foam-forming floating antacid product. No claim is made that alginic acid has any antacid activity. Heretofore alginic acid had been reviewed and classified as an active antacid ingredient. Hence it has been necessary to reassess the petition in light of the sponsor's position regarding alginic acid.

For these reasons it has taken longer than anticipated to evaluate the test results that have been submitted in support of the three petitions to amend the antacid monograph, and because this evaluation is still ongoing, the Commissioner concludes that the final classification of Category III conditions for which no test results have

been submitted should not be further delayed.

The Commissioner will set forth his findings on the three petitions to amend the antacid monograph in separate FEDERAL REGISTER publications as soon as review of the petitions is completed.

This notice, therefore, constitutes a final determination that the ingredients, combinations of ingredients, and labeling claims discussed below are classified in Category II for OTC antacid drug products and thus may not be marketed in interstate commerce unless they are the subject of a new drug application approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

In the preamble to the June 4, 1974 (39 FR 19873-19874) final order establishing part 331, the Commissioner determined that adequate and reliable scientific evidence was not available to permit final classification of the following OTC antacid active ingredients: Alginic acid, attapulgite (activated), charcoal (activated), gastric mucin, kaolin, methylcellulose, pectin, and carboxymethylcellulose, and these ingredients were placed in Category III to allow for further testing.

Alginic acid, as discussed above, is included in one of the petitions to amend the antacid monograph and its status is, therefore, not affected by this notice. No data were submitted during the testing period in support of any of the other Category III ingredients identified above. As a result, none of those ingredients is generally recognized as safe and effective for antacid use; they are regarded as new drugs as defined in section 201(p) of the act (21 U.S.C. 321(p)) requiring approved new drug applications prior to marketing for antacid use.

Included among the Category III labeling claims identified in the preamble to the June 4, 1974 (39 FR 19874) antacid final order were claims alleging relief of the following symptoms not known to be related to acidity of gastric contents: Indigestion, gas, upper abdominal pressure, full feeling, nausea, excessive eructations (belching), and upset stomach. The Commissioner concluded that these symptoms were vague, most were poorly understood as to pathophysiological mechanisms, and none had been shown by adequate and reliable scientific evidence to be caused or alleviated by changes in gastric acidity.

Other claims or indications linking certain signs and symptoms with gastric acidity were placed in Category III on the ground that these claims were unproven. The relationship of these signs and symptoms to gastric acidity was unknown or dubious, with no adequate and reliable scientific evidence to support the use of antacids to relieve them. The following signs and symptoms were placed in Category III for this reason: Sour breath, upper abdominal pressure, full feeling, nausea, stomach distress, indigestion, upset stomach, and excessive eructations. The Commissioner concurred with the Advisory Review Panel on OTC Antacid Drug Products that these claims or indications encouraged the user to draw conclusions as to the cause or intermediation of such symptoms, conclusions that even members of the medical profession were incapable of drawing at that time.

Other claims relating to physical or chemical properties were placed in Category III on the ground that the currently available evidence was inadequate to support the conclusion that the properties contributed to the relief of upper gastrointestinal symptoms. The properties were: Floating, coating, defoaming, demulcent, and carminative. The Commissioner advised in the preamble to the June 4, 1974 (39 FR 19874) antacid final order that continued use of these claims, or ones closely allied to them, would require additional studies both to confirm the claimed specific action and to demonstrate its clinical significance. The Commissioner will defer a final decision on the term "floating" until the review of the petition to amend the antacid final order to include a foam-forming floating antacid product in Category I has been completed.

No data was submitted during the testing period in support of any Category III antacid claim or property except "upset stomach" and "floating."

Accordingly, the following untested claims that were previously classified as Category III are now placed into Category II when used for OTC antacid drug products: Indigestion, gas, upper abdominal pressure, full feeling, nausea, excessive eructations (belching), sour breath, stomach distress, coating, defoaming, demulcent, and carminative. Antacid drug products that are initially introduced or delivered for introduction into interstate commerce after the effective date of this notice bearing these claims in their labeling will be in violation of sections 502 and 505 of the act (21 U.S.C. 352 and 355) and, therefore, subject to regulatory action.

The Commissioner is aware that confidentiality was requested by Marion Laboratories, Inc., Miles Laboratories, Inc., and Warner-Lambert Co., for information in their petitions submitted to amend the final order on OTC antacid products. The issue of whether such information is entitled to confidential status was fully discussed in paragraph 10 of the preamble to the April 12, 1977, amendments to § 330.10(a). However, to assure that there is no misunderstanding, the Commissioner reemphasizes several points made regarding the disclosability of all safety and effectiveness information in submissions to amend OTC monographs. General recognition of safety and effectiveness for a Category III product subject to a petition to amend a monograph must be based on data and information that are in the public domain and therefore available to the community of experts without restriction. Confidentiality of data relating to safety and effectiveness is incompatible with Category III status, which looks toward establishment of general recognition of such safety and effectiveness. General recognition of safety and effectiveness cannot, as a definitional matter, be shown by reference to confidential material (see *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 632 (1973); *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973)), and, therefore, all safety and effectiveness data and information submitted with a petition to amend a monograph to include a condition previously classified in Category III will become publicly available when the petition is received (see the FEDERAL REGISTER of April 12, 1977). With respect to the three petitions submitted to amend the antacid monograph, they will become publicly available on September 5, 1978. Any other approach would be inconsistent with both the goal and procedures of the OTC drug review. These petitions shall be maintained in a permanent file for public inspection in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

The effective date of this notice is March 5, 1979. After that date, no person will be permitted to initially introduce or deliver for introduction into interstate commerce any OTC antacid drug product not included in the monograph established in 21 CFR Part 331, except as noted herein.

Dated: August 29, 1978.

JOSEPH P. HILE,
Associate Commissioner for Regulatory Affairs.

[FR Doc. 78-24914 Filed 9-1-78; 8:45 am]

[4110-02]

Office of Education

NATIONAL ADVISORY COUNCIL ON EXTENSION AND CONTINUING EDUCATION

Meeting

AGENCY: National Advisory Council on Extension and Continuing Education.

ACTION: Notice of meeting.