DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 130]

OVER-THE-COUNTER DRUGS GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

Tentative Final Order for Antacid Products

In the FEDERAL REGISTER of April 5, 1973 (38 FR 8714), the Commissioner of Food and Drugs, pursuant to § 130.301(a)(6) ((21 CFR 130.301(a)(6))), published a proposed monograph on over-the-counter (OTC) antacid drugs.

Interested persons were invited to submit comments on the proposal within 60 days. Twenty-seven such comments were received. For thirty days after the final day for submission of comments, reply comments could be filed with the Hearing Clerk in response to comments filed in the initial 60-day period. Eleven reply comments were received. A transcript of a Senate hearing held by the Subcommittee on Monopoly of the Select Committee on Small Business, chaired by Senator Nelson, on June 6, 1973, during which testimony was presented on OTC antacid drugs, was filed with the Hearing Clerk and has been considered in the same way as all other comments.

In accordance with § 130.301(a)(2) all data and information submitted with respect to OTC antacid drugs for consideration by the Advisory Review Panel has been put on public display at the office of the Hearing Clerk, Food and Drug Administration, Rm. 6–86, 5600 Fishers Lane, Rockville, Maryland 20852, after deletion of a small amount of trade secret information.

The Commissioner has reviewed the Report and Monograph and all comments and reply commtne nasd ments and reply comments and has reached the following conclusions.

GENERAL COMMENTS

1. One comment stated that the proposal establishing a monograph for OTC antacid products is invalid because Executive Order 11671 was violated in that no notice appeared in the FEDERAL REGISTER or in the local media stating the purpose, membership, or activities of the Panel, including the dates, places, and agenda of open meetings.

The Food and Drug Administration published in its Public Advisory Committee publication [DHEW Publication 1972 0–464–928] the authority, structure, function of the Panel and names and addresses of the Panel Chairman and its members. The establishment and activities of the Panel, both prospectively and retrospectively, were extensively reported in the trade and public press. A call for submission of data and views was published in the FEDERAL REGISTER of January 5, 1972 (37 FR 102). An opportunity for a personal appearance before the Panel was granted to all interested persons making such a request and numerous persons met with the Panel, including representatives from industry. No request to appear before the Panel was denied. Information on meetings was regularly carried in the professional and trade press. The comment does not contend that any interested person was not aware of the existence of the Panel or did not receive notice of meetings or was not apprised of an opportunity to appear before the Panel. Thus, there is no basis for concluding that Executive Order 11671 was violated or that the monograph is invalid because of the failure to provide interested persons with an opportunity to make their views known to the Panel.

2. There was comment that the Food and Drug Administration has no authority pursuant to the OTC drug review to determine which drugs are generally recognized as safe and effective and not misbranded where there has been a prior court adjudication that a particular product is neither adulterated nor misbranded.

A prior court adjudication is not determinative of the legality of a drug at all times in the future. The OTC drug review considers data and information not previously available and reevaluates prior data in light of the most current medical and scientific information. Accordingly, the results of this review are regarded by the Food and Drug Administration as superseding all earlier administrative or court determinations.

3. Numerous comments contended that the agency does not have the authority under the Federal Food, Drug, and Cosmetic Act to establish substantive rules. This subject was dealt with in some detail in paragraphs 85 through 91 of the preamble to the procedures for classification of over-the-counter drugs published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), and the Commissioner reiterates the conclusions stated there. Legal decisions handed down since then have sustained the Commissioner's authority to issue substantive regulations establishing the legal status of OTC drugs.

(United States v. Articles of Food and Drug * * * Coli-trol 80 Medicated, N.D. Ga., Cosm. L. Rep. par. 40,837 (1973). United States v. Bentex Pharmaceuticals, 412 U.S. 645, 93 SCt 2488 (1973). Warner Lambert v. FTC D.D.C. (Civil No. 652–73), decided June 14, 1973.)

4. There was comment that there are no data to suggest that the proposed labeling changes will be complied with and have their intended effect, or that they will even be read.

The Food and Drug Administration is presently engaged in studies to assess the understanding and acceptability by the public of current drug labeling and to develop new labeling formats that can lead to easier reading, improved comprehension, and better use of OTC drug labeling. Other groups, including consumer, industry, and advertising groups are also concerned with developing product labeling that can be and will be read and followed by the consumer. The Commissioner welcomes their cooperation on this matter.

5. There was comment that required relabeling should be supplemented by corrective media advertising to counter the effects of longstanding inappropriate advertised claims.

The Food and Drug Administration does not regulate OTC drug advertising. As the comment correctly noted, this is a responsibility of the Federal Trade Commission. The Food and Drug Administration maintains close liaison with the Commission on relevant matters concerning the over-the-counter drug efficacy review and will inform the Commission about all required drug labeling changes.

6. One comment suggested that consumer participation in panel deliberations by a non-voting liaison member should not be a substitute for making the decision making process more accessible to the general public.

This matter was fully discussed in paragraph 37 of the preamble to the procedural regulations published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464). Public participation and accessibility to decisions and data are fundamental principles of the OTC drug review. Any interested person may submit written presentations to the Panel. In addition to continuous and direct participation by consumer and industry liaison members, a period of time has been set aside at each panel meeting for interested persons to present relevant information in open session. No request to appear before a panel has been denied by any panel. Minutes of each panel meeting, including interim conclusions of the panel, have been made available to interested persons. All data submitted to the panel, with the exception of a very small amount of confidential trade secrets, has been made available to the public after the Panel report has been published. All interested persons may then offer additional written comments, reply comments, and objections; may request a hearing before the Commissioner; and may appeal the final monograph to the courts. The public therefore has ample opportunity to participate in this process.

7. There was comment that the circulation of the draft proposed report to the consumer and industry liaison member, and thus to all interested members of the public, was not provided for in § 130.301(a) and that, if it was a helpful procedure, it should be added to the regulations and a proposal should be published in the FEDERAL REGISTER.

The Food and Drug Administration has organized the review panels to get independent scientific judgments on the safety, effectiveness, and proper labeling of OTC drugs. The Commissioner believes that the panels should have maximum discretion in accomplishing their task. One panel's decision to circulate an early draft of their proposed report should not require other panels to follow the same procedure. The regulations provide for two publications of the monograph in the FEDERAL REGISTER before it becomes final.

8. One comment stated that it was not possible to comment on the report and proposed monograph because the Panel's summary minutes were cryptic and no public transcript was available.

The object of writing and making available summary minutes was to maintain a full and accurate record of the Panel's reasoning and judgments and to minimize the circulation of speculative and misleading information as to the current status of the review. The minutes were read and approved by all members of the Panel and were then made available to the public. The Commissioner has reviewed the Panel's minutes and concludes that, when viewed in the light of the report and the data on file with the Hearing Clerk, on which the Panel relied, they amply serve their intended purpose. The public record is sufficient for any person to comment meaningfully on the proposed monograph.

9. It was stated that the publication of the proposed monograph without review by the Commissioner is not consistent with the procedure set forth in § 130.301 (a)(6).

The Commissioner concluded that the public interest was best served in the case of the proposed Antacid Monograph by publishing the document exactly as received by the Food and Drug Administration and to defer evaluation and any amendments until after the initial comment period. With future reports, because of length or types of recommendations he may wish to evaluate the report before publication. The deferral of his review in this case does not adversely affect the procedure established in § 130.301(a)(6) nor is it prohibited by the provisions of that section. To clarify this matter, however, the Commissioner is publishing a proposal to amend the regulations in order explicitly to confirm the propriety of this procedure elsewhere in this issue of the FEDERAL REGISTER.

10. The greatest number of comments concerned the proposed effective date of the final monograph after publication in the FEDERAL REGISTER. Some felt six months was too long considering the lengthly review procedures, while others claimed the time was inadequate to arrange for formulation and labeling changes. Some suggested a year to eighteen months.

Manufacturers and other interested parties have had full access to interim and final conclusions of the panel. There is ample time to develop new labeling and formulations before the final regulations issue. The Commissioner concludes that it is reasonable to require all manufacturers to be in compliance within six months of publication of a final monograph.

11. There was comment that the Commissioner ignored his responsibility to make a determination of the conditions that would result in an OTC product not being generally recognized as safe and effective or would result in misbranding or where data are insufficient to permit classification at this time.

The Commissioner proposed in that notice to adopt the findings in the panel report, including the "conditions under which antacid products are not generally recognized as safe and effective or are misbranded" (Category II), and the conditions where data are "insufficient to permit final classification at this time" (Category III). His tentative final conclusions on these issues are contained in this notice.

12. There was comment that all drugs which are not generally recognized as safe and effective or are misbranded (Category II) should be removed from the market immediately upon publication of the final monograph unless a new drug application (NDA) has been filed in support of the drug.

Since the final monograph will not become known until publication, manufacturers cannot be expected to have definite knowledge of the ingredients to be removed from the market until that date. Nor can tests that have already begun necessarily be completed by then. Sufficient time should be allowed for a manufacturer to reformulate his product, remove it from the market, or file an NDA. The Commissioner concludes that a 6-month period is adequate for these purposes.

13. There was comment proposing that in the future the Category III ingredients be listed as part of the proposed monograph and published in the FEDERAL REGISTER including a list of tests which the manufacturers would need to start immediately in order to transfer the ingredient to Category I. This comment argued that such testing should be completed within the 6-month implementation period.

The Category III ingredients were listed in the proposal, and their manufacturers and users are therefore on notice about the need for additional testing. All interested persons must of course be given an opportunity to comment on the need for further testing. Whenever feasible, appropriate testing for Category III ingredients will be indicated. Upon further consideration, the Commissioner concludes that a two year period after publication of the final monograph is reasonable for completion of all required additional testing for the Category III ingredients covered by the Antacid monograph.

14. It was proposed that manufacturers who market products containing Category III ingredients change their labeling immediately. There were some comments that the industry should not be allowed two years to prove false and misleading claims and that Category III ingredients should be removed immediately.

The Commissioner has reviewed this matter thoroughly and concurs with the Panel's recommendation that Category II conditions should be eliminated within 6 months of publication of the final monograph but that Category III conditions may be continued for up to two years conditioned upon further testing. The Commissioner knows of no health hazard that would result from this interim use of Category III ingredients and conditions of use.

15. There was comment that the Food and Drug Administration must become involved in consumer education to alert the purchaser of OTC drugs to the labeling changes.

The Commissioner agrees. In addition to undertaking the studies mentioned under paragraph 4, the Food and Drug Administration is planning an extensive multi-media campaign to alert consumers to formulation and labeling changes for OTC drugs.

16. One comment suggested that a third class of drugs should be formed. This class would be OTC drugs available only from a pharmacist, and for which the pharmacist would maintain a patient dispensing record.

This matter is not within the purview of the OTC drug review. The purpose of the review is to determine those drugs that may safely and effectively be purchased and used without a physician's prescription and supervision regardless of the channel of distribution. All drugs contained in the final monographs will meet those criteria. Comments on a third class of drugs are therefore not pertinent to the review.

17. Numerous comments were received to the effect that the language for warnings, directions for use, and indications should only be guidelines and that language of similar intent should be acceptable.

The use of dissimilar labeling in situations involving identical uses and hazards would cause consumer confusion and could lead to deception and unsafe use. Use of the same language will reduce the likelihood of confusion and harm. The Commissioner therefore concludes that the labeling specified in the monograph will be mandatory.

18. There was comment that no inventory recall of noncomplying products should be required after the effective date of the final order.

The Food and Drug Administration at this time sees no need to recall any OTC antacid product after publication of the final monograph. If the Agency finds that a manufacturer, distributor or buyer has an inventory of a size that is obviously intended to prolong the marketing of a Category II product, or concludes that a hazard exists, appropriate action will be taken.

19. One of the most frequent comments was that clinical investigators are not enthusiastic about studies on OTC drugs because they are subjective in nature, difficult to perform, and retrospective in approach, and therefore not popular with scientific journals. It was contended that this makes it difficult to obtain adequate scientific data on Category III ingredients.

The Food and Drug Administration recognizes that OTC drug studies are often more difficult to undertake than those involving prescription drugs. OTC drug studies are principally concerned with measuring symptomatic relief, requiring methods that are more subjective than those used to measure the resolution of a disease condition. In all cases, however, such tests are entirely feasible and, indeed, have in many cases been conducted in the past. Nor is difficulty in performing studies sufficient justification for retaining on the market drugs the safety and effectiveness of which are inadequately documented.

20. There was comment that the preamble and proposal did not state how new data on Category III ingredients are to be reviewed.

The Food and Drug Administration is establishing an Implementation Unit within the OTC drug staff to advise interested persons on the kinds and extent of research needed to substantiate the safety and effectiveness of Categtory III conditions. The Implementation Unit will consult with the Office of Scientific Evaluation and may request the assistance of the OTC Antacid Review Panel and appropriate Bureau of Drugs advisory committees.

21. There was comment that the status of Category III ingredients, individually and in combination, has not been stated.

Section 130.301(a)(6) and the proposal clearly state that any Category III ingredient or condition or combination with other ingredients in Category I or III may continue to be marketed if testing for proof of efficacy is in fact undertaken during the period provided. Products that claim to be antacids must meet the acid neutralizing test during this two-year period, but any products which do not contain acid-reducing claims need not modify their claims until the two-year period has terminated.

22. There was comment that undertaking tests and studies should not be a condition for continued marketing of drugs in Category III.

The proposal included this condition for the continued marketing of Category III drugs because otherwise there is no justification whatever for such marketing. The Commissioner concludes that it would be unreasonable and unwarranted to permit the continued use of unsubstantiated conditions during the two year period provided for additional testing if in fact no such testing is being undertaken to obtain the necessary substantiation.

23. There was a comment that the monograph failed to include mildly alkaline products such as alkaline mineral waters.

No evidence was presented to the Panel or with the comments to show that such ingredients or products containing them are safe and effective as antacids. The Commissioner concludes that they are neither proven nor generally recognized as safe and effective for use in antacid therapy and are thus misbranded for such use.

COMMENTS ON THE REPORT

24. There was comment that the Panel exceeded its charge in recommending the development of an in vivo standard for OTC antacid drugs.

The Food and Drug Administration has asked the advisory review panels for their scientific judgment and expertise. To make sure that independent judgment is obtained, the Food and Drug Administration has stressed to all the panels that the Agency will consider any advice they offer. This recommendation was well within the Panel's charge. The Food and Drug Administration will investigate further to determine whether an in vivo standard is feasible.

25. There was comment that an antacid product containing alginic acid is safe and effective for the symptomatic treatment of reflux esophagitis (a condition with the symptom of heartburn caused by the regurgitation of stomach acid). Three published and one unpublished studies were filed in support for that indication. One article had been previously submitted to the Panel and evaluates the effectiveness of an antacid/alginic acid product in the treatment of reflux esophagitis over a one month period (Journal of the American Geriatrics Society 20(7): 293–304, 1972). The findings are merely summarized and are largely testimonial in nature. The study lacks a well defined protocol and fails to include a non-alginic acid containing antacid control. Additional data, not previously submitted to the Panel, includes an unpublished study involving 47 patients with radiographic evidence of hiatal hernia and symptoms of reflux esophagitis. Two antacids, one containing alginic acid, were compared in the treatment of symptomatology associated with reflux esophagitis over a 4-week period. The findings indicate improvement for the symptom epigastric to retrosternal distress for the antacid/alginic acid product but little difference between the combination and an antacid in treating regurgitation and epigastric gas. However, the results are inconclusive for insufficient data was submitted, including lack of baseline values, incomplete follow-up examinations and the inclusion of several patients with a normal esophagus. In a published double-blind cross-over study (Current Medical Research and Opinion 1(2): 63–69, 1972), an alginate/antacid compound was compared to alginate without antacid and a placebo in relieving regurgitation and heartburn. Relief of symptoms is reported with the alginate/antacid compound but alginate alone was only marginally better than placebo. Here again the findings are inconclusive for an antacid control was not included and patients apparently went from one treatment to another without allowing for an interval between treatments or re-evaluation at the end of each treatment period. In another submitted article involving a study in infants with persistent vomiting, the results indicate a reduction in vomiting when the alginic acid containing antacid is included in the prepared baby formula. The study fails to include sufficient information about previous treatments described in the article or compare the ingredient with a placebo (Australian Pediatric Journal 8: 279–281, 1972). The Commissioner concludes that the additional studies were not well controlled and based upon all of the data submitted affirms the Panel's conclusion that alginic acid has not been shown to be effective and thus should remain in Category III, pending further study.

26. There was comment that the labeling "Do not take this product concurrently with a prescription drug except on the advice of your physician or pharmacist" should not be restricted to charcoal, but should be included for any other OTC drugs where side effects and drug interactions may occur.

The antacid review panel did not list any other drug interactions of which the consumer should be aware, nor was there sufficient documentation of any such interaction in comments submitted on the proposal. Pursuant to another comment, the Commissioner is adopting elsewhere in this issue of the FEDERAL REGISTER, a standard drug interaction warning to be used whenever a panel determines that it is appropriate.

27. There was comment that inclusion of the pharmacist in the label warning against concurrent use of charcoal and prescription drugs is inappropriate because pharmacists may not be sufficiently knowledgeable about drug interactions and because such advice may contravene certain State laws.

The Commissioner believes that the pharmacist is an important member of the health care team. Neither the knowledge nor competence of the pharmacist nor the precise role of the pharmacist in the organization and delivery of health care is at issue in this matter. His precise role in clinical health care, however, is the subject of intense interest and debate as part of the larger issue of the future of the entire health care delivery system. The Commissioner concludes that such an important matter should be resolved in the context of broad health policy deliberations and not as a part of the OTC drug review, and thus that no reference should be made to pharmacists in OTC drug labeling at this time. Once the larger issues of health care delivery have been resolved, the Commissioner will reconsider this matter.

28. There were comments that the Panel did not spend sufficient time reviewing inactive ingredients and that a separate OTC panel should review inactive ingredients.

The large number of ingredients and the amonut of data to be reviewed by the Panel made it necessary to exclude routine consideration of inactive ingredients in the review. Pursuant to § 130.301, the call for data requested information only on active ingredients. The panel did review two inactive ingredients felt to be of special importance and it is anticipated that future panels will also give special attention to some inactive ingredients. The Commissioner has asked the National Advisory Drug Committee to consider the advisability of listing inactive ingredients on OTC drug labels.

29. There were a number of comments about the "Clinical Toxicological Data" recommendation of the Panel in its section on "Data Pertinent to Antacid Ingredient Evaluation."

The Panel recommended that an effort be made to collect any pertinent data that might be available from poison control or drug information systems on the lethal dose in humans. These recommendations were intended to be used by the Food and Drug Administration and the industry as a guide to needed information.

COMMENTS ON THE PROPOSED MONOGRAPH

ACTIVE INGREDIENTS

30. A number of comments stated that requiring an OTC antacid ingredient to contribute at least 25 percent of the acid neutralizing capacity was not based on scientific fact, and that it should be deleted or the 10-percent figure originally proposed in the minutes should be adopted.

The 25-percent figure was based on the conclusion that an ingredient which contributes less than that reaches the point where its contribution as an active ingredient is insignificant. To require no minimum contribution at all would be to allow the use of amounts so small as to be misleading and deceptive to the consumer. Moreover, small percentage contributions, accompanied by a proliferation of ingredients in various formulations, would make difficult the evaluation of safety and effectiveness and the identification of possible side effects. It would be unreasonable and deceptive to permit the use of 10 active ingredients, each contributing only 10 percent of the effects. Use of a requirement less than 25 percent would permit inclusion of ingredients solely for promotional purposes. The Commissioner therefore affirms the Panel's judgment that a minimum 25-percent contribution to acid neutralizing capacity by each active ingredient is a reasonable requirement.

31. There was comment that the Panel should have established a procedure for allowing a product to be marketed as an antacid where it is effective but does not pass the acid neutralizing test.

Such an ingredient has not been identified to the Food and Drug Administration. If and when this circumstance arises, the monograph can be amended as provided in § 130.301(a)(11).

32. There were numerous comments that the acid neutralizing test should not be adopted until it has been fully validated by an appropriate body of scientific experts.

The Commissioner agrees. The Food and Drug Administration is conducting appropriate studies to validate the test. No comment offered persuasive evidence showing that the proposed test is invalid.

33. One comment stated that a tablet disintegration test is necessary because a tablet may pass the acid neutralizing test and still not be dissolved.

Passing the acid neutralizing test in fifteen minutes does not exempt the official tablets from passing the standard U.S.P. tablet disintegration test. The acid neutralizing test is an additional standard and does not supplant other required standards. It should be noted, however, that the Panel concluded that any tablet that passed the acid neutralizing test would be disintegrated.

34. A comment contended that the acid neutralizing test would favor fast-acting strong alkaline ingredients and that this could result in undesirable "acid rebound."

The Commissioner concluded there is little support for the acid rebound theory, and there is no reason to believe the test favors strong alkaline products to the disadvantage of other antacid ingredients. The Commissioner believes that the acid neutralizing capacity is only one of many factors that a physician will consider in selecting an effective antacid for his patient.

35. The fifteen minute test duration was criticized because an antacid may be in the stomach much longer.

The test takes into consideration the fact that the fasting stomach retains an antacid for about fifteen minutes. Unless it is effective in that time, the patient may not obtain relief. The fact that an antacid may have a prolonged duration of action is one of the reasons why the acid neutralizing value is only one factor to be considered in antacid effectiveness and may be used only in ethical labeling.

36. The pH 3.5 endpoint of the test was criticized as unduly restrictive since the pH necessary to relieve upper gastrointestinal symptoms is not known.

The Commissioner concurs in the Panel's conclusion that an increase in pH to 3.5 is an appropriate standard for supporting a claim of decreased stomach acidity. No data were presented to dispute that conclusion.

37. The U.S.P. has established a method for assaying antacids. One comment stated that this method should be used instead of the acid neutralizing test in the proposed monograph.

The two U.S.P. acid consuming capacity tests are concerned only with total consumption and not with the duration of activity. If a drug takes an hour to neutralize a given amount of acid but is in the stomach for only fifteen minutes, its therapeutic value is highly questionable. The proposed test is designed to take both neutralizing capacity and time into account.

38. There was comment that the in vitro acid neutralizing test will discourage research in the development and evaluation of new antacids.

The Commissioner concludes that nothing in the test or in any other provision of the proposed monograph should discourage or retard research in antacid therapy. On the contrary, the test should serve to kindle new ideas about and methods of measuring the effectiveness of such treatment. In accordance with the Panel's recommendation, the Commissioner also intends to explore reliable in vivo tests of effectiveness for antacids.

39. A comment stated that the stirring speed should be measured by a photo-tachometer or similar device.

The Commissioner agrees and the tentative final monograph so provides.

40. A comment stated that the stirring speed should be increased to 500 RPM or a surfactant used because the slower speeds result in floating particles.

The Commissioner agrees and the tentative final monograph so provides.

41. Another comment suggested that the pH meter should be calibrated between 1.1 and at least 7 to permit accurate measurements.

The Commissioner concludes that the method of calibration proposed by the Panel is satisfactory. No data were submitted to support the comment.

42. It was commented that the grinding and sieving of double layer tablets following the procedure results in disproportionately richer mixtures.

The Commissioner recognizes that modifications of the method of preparation of the product may be warranted. It is the responsibility of the manufacturer to propose an alternative method through a petition pursuant to § 130.301 (a)(11).

43. A comment stated that the equipment specifications should be amended to substitute a rotating bottle apparatus for magnetic stirrer because of better temperature control and stirring speed reliability.

The Commissioner concludes that the rotating bottle method would be awkward for use in this test. The comment included no data to show that such a method would significantly increase reliability.

44. A comment suggested that one normal HCl is too strong in that it causes viscous antacids to stick to electrodes and carbonated products to foam. The comment stated that 0.1N HCl should be substituted since it represents a concentration of acid more in keeping with the acid concentration of the stomach.

The Commissioner concludes that either 0.1N or 1.0N HCl may be used, and the tentative final order so provides.

45. There was comment that, since aluminum compounds may interfere with prescription medications, they should no longer be marketed.

Aluminum ingredients are safe and effective as antacids. The evidence that they may decrease the absorption of certain prescription products is uncertain. Thus, to eliminate this antacid ingredient would be inappropriate in view of the current lack of evidence that a drug interaction exists. The Commissioner welcomes any additional evidence on this issue, and will take appropriate action if drug interaction is shown.

46. There was comment that this subsection could be construed to exclude aluminum hydroxide.

That was not the intent and the language has been clarified in the tentative final monograph.

47. There was comment that the provisions concerning bicarbonates should be deleted because these ions are sufficiently addressed in the sodium subsection.

The limits on the bicarbonate ion involve consideration of potential alkalosis whereas the primary concern with the sodium ion relates to hypertension. The Commissioner concludes that, for this reason, these different species are properly treated as distinct entities.

48. There was comment that it should be made clear that sodium carbonate is only to be used as a component of effervescent tablets.

This provision has been so revised in the tentative final monograph.

INDICATIONS

49. There were a number of comments that the four allowed terms, "heartburn", "sour stomach", "acid indigestion", and "antacid", lack meaning to the consumer and are restrictive beyond the intent of § 130.301(4)(v) which requires terms "likely to be read and understood by the ordinary individual, including individuals of low comprehension". One of the comments submitted a national probability study of consumer language to show that terms other than those designated by the Panel are used by the consumer to designate the symptom for which he takes an antacid. Five nationally advertized products were used in the study. They were an antacid-analgesic, an antacid-flatulent, an antacid-diarrheal, and two antacids. About 1,000 heads of households were contacted. It was reported that "upset stomach" was the leading term used by the consumer irrespective of sex, age, income level or education.

The Commissioner concludes that the study is not relevant to the question whether acid indigestion also encompasses an upset stomach. Of the five products selected, two have been heavily advertised for "upset stomach", thus promoting the misconception that an antacid is useful for this purpose. These products have very different formulations, which would not be effective under all of the same conditions of use. It is further evident from the terms used by the consumers who participated in the study that a great deal of consumer confusion exists, possibly because of overzealous promotion.

The Commissioner concludes that the terms recommended by the Panel fully meet the intent of the regulation. Allowing each manufacturer to select the words to be used would result in continued consumer confusion and deception. The terms proposed by the Panel all relate to symptoms caused by excess gastric acidity, the sole condition for which antacids are generally recognized as effective. Other proposed terms such as "stomach upset" have different meanings to different individuals ranging from acid indigestion to nausea, cramps, and diarrhea, for which an antacid is ineffective. The Commissioner concludes that the evidence presented does not justify expansion of the present number of permitted terms.

WARNINGS

50. There was a comment that the warning statements under subparagraphs (1) and (2) of paragraph (c) should be combined.

The Commissioner agrees and the tentative final monograph so provides.

51. There was comment that the language proposed for limiting use of the product at the maximum dosage for two weeks is inappropriate since it implies a question about the product's safety, when in fact it is the patient's continuing symptoms that are of concern.

The Commissioner concludes that the phrase proposed by the comment, deleting the maximum dosage statement, would not be as complete or meaningful to the consumer as the Panel's language. The proposed language neither states nor implies a safety problem.

52. There was comment that a 5-percent incidence of constipation or laxation as a determinant of the warning requirement is arbitrary and should be replaced with a term such as "significant proportion" of users. No data were submitted to support a different figure.

The Commissioner concludes that deletion of the 5-percent figure would significantly lessen the ability to enforce the labeling statement. An endless debate could be engaged about the significance of any particular incidence, and different manufacturers would use different figures. The Commissioner concurs with the Panel's conclusion that 5 percent is appropriate in the absence of more specific data or expert opinion establishing a different figure.

53. There was comment that the sodium warning directed at antacid users on salt-restricted diets, proposed for drugs containing more than 5 milliequivalents, is inappropriate and should be deleted. The comment also stated that, if the warning is retained, it should apply only to daily dosages in excess of 10 milliequivalents.

While it is generally true that sodium-containing antacids would not materially interfere with a low-salt regimen, OTC antacids are often used under medical supervision at higher than recommended doses. Patients should have information about sodium content in the event that the physician's directions are not fully understood or the patient changes antacids on his own volition. The Commissioner therefore concludes that the proposed sodium warning is appropriate.

DIRECTIONS FOR USE

54. There was comment that the directions for use should include the recommended total number of administrations in a given time period (e.g. "four times a day") as an alternative to single doses in a given time period (e.g. "every four hours").

The Commissioner agrees and the tentative final monograph so provides.

STATEMENT OF ACTIVE INGREDIENTS

55. There were several comments commending the Panel for recommending that the labeling of all OTC antacid products be required to include a quantitative listing of each active ingredient. There were also many comments citing 21 U.S.C. 352(e)(1)(A), which provides for quantitative ingredient labeling only for prescription drugs.

The Food and Drug Administration concurs that the statute presently requires quantitative ingredient labeling only for prescription drugs. The National Advisory Drug Committee has recommended that all OTC drugs be labeled with a quantitative statement of the active ingredients. No comments offered persuasive reasons why this is not in the public interest. Accordingly, the Commissioner has deleted the provision relating only to antacid drugs and has included such a provision, as a recommendation, in the general conditions for all OTC drugs established under new § 130.302, published elsewhere in this issue of the FEDERAL REGISTER. The Commissioner urges manufacturers to comply with this request without the necessity for a change in the statute.

ETHICAL LABELING

56. There was comment that the warning statements appearing on OTC products should not be included in ethical labeling.

The Commissioner concludes that such an approach is without merit, since it would deprive the physician of important information that he can expect his patient to have in hand.

57. There were numerous comments that the acid neutralizing capacity of an OTC antacid should appear on all OTC labeling. Others argued that this information should not even be included in ethical labeling because it would encourage a competitive "numbers game."

The Commissioner agrees with the Panel that the physician should be supplied with as much relevant data as possible, including the acid neutralizing capacity. However, inclusion of this technical information on the consumer label could result more in confusion than enlightenment, and could result in unwarranted consumer reliance solely upon this information as an indication of relative effectiveness. If there is evidence in the future that shows that such information could be placed in a labeling format useful to the consumer, the Commissioner will reconsider this decision.

58. Another comment suggested that a label statement of a suitable range for the neutralizing capacity be permitted, since variations may occur between manufactured batches and after extended shelf life.

The Commissioner realizes that variations may occur and therefore concludes that such information should be permitted in the form of a range. A product should not be labeled with an acid neutralizing capacity value exceeding 10 percent of the determined lower limit. If the acid neutralizing capacity of a product is reduced with extended shelf life, ethical labeling may indicate the value at the time of manufacture and/or what can be reasonably expected after a specified period of time. No product may be marketed with an acid neutralizing capacity below 5 meq. The tentative final order has been so revised.

59. Some comments were concerned that the Panel recognized that aluminum and other antacids may interfere with prescription drug absorption but proposed inclusion of such information only in ethical labeling, not in the consumer labeling where such information is also needed.

The Commissioner concurs with the Panel that the evidence of drug interaction is fragmentary and conflicting

and requires explanation to the consumer by a physician or pharmacist where appropriate. Since the physician or pharmacist should already be aware of such information they are the proper persons to be informed of possible drug interactions through ethical labeling. If a drug interaction is proved, the Commissioner will reopen the question of proper consumer labeling.

60. It was recommended that the ethical labeling claims for antacids be expanded to include gastric hyperacidity and hiatal hernia.

The Commissioner concludes that the terms "hiatal hernia" and "gastric hyperacidity" may be included in ethical labeling and has so provided in the tentative final monograph.

COMBINATIONS WITH NONANTACID ACTIVE INGREDIENTS

61. There was comment that the laxative ingredient in the antacid/laxative combination should be listed on the label.

This provision has been so revised in the tentative final order.

62. There was comment that antacid-salicylate combinations have been labeled and promoted for many years primarily for antacid use alone, and that labeling changes are not sufficient to assure the informed and proper use of these products. There were several comments that where an antacid-salicylate combination had been labeled as an antacid, removal from the market or reformulation to exclude salicylates were the only effective means of protecting the consumer.

The Panel concluded and the Commissioner concurs that this combination should not be used for antacid purposes alone. The proposed labeling limits the combination for use where the individual has symptoms requiring both an analgesic and an antacid. For continued marketing these limitations must be clearly identified in all future promotional efforts. The Commissioner concludes that proper labeling in the future will be sufficient to assure proper use of such combination products. The Federal Trade Commission has responsibility for assuring the propriety of future advertising of these products. The Commissioner also concludes that there is insufficient data to warrant removal of the combination or the salicylate from the combination, even though it was labeled in the past as an antacid.

63. All comments recognize that aspirin causes gastrointestinal bleeding, and few questioned the claim that the combination of an antacid salicylate causes less gastric bleeding in normal individuals than unbuffered aspirin. Many contended that there is no evidence to support the use of a salicylate-containing product in patients with gastric disease and therefore the combination should be reformulated as an antacid or labeled and used exclusively as an analgesic.

The Commissioner agrees that OTC antacid products, including combinations, should not be used by patients with gastric diseases except on the advice of a physician, but he concurs with the Panel that there is a significant target population for which the antacid-salicylate combination provides rational concurrent therapy, (e.g., headache and acid indigestion). In fact, the combination is probably a safer more effective medication because it is buffered. The Commissioner therefore concludes that the combinations should not have to be reformulated as an antacid or labeled exclusively as an analgesic.

64. There was also comment that the Panel was overly restrictive in not recognizing the potential for analgesics in relieving certain transient symptoms of upper gastrointestinal distress. It was noted that the Panel recognized that the etiology of upper gastrointestinal distress is not well understood. One comment suggested that these symptoms of gastric distress may be associated with inflammatory reactions and that analgesics may be beneficial in reducing gastric inflammation and pain.

The Commissioner finds the proposals conjectural and at this time concludes that there is a lack of substantial evidence to support such claims. The Commissioner welcomes any scientific data that would adequately demonstrate the effectiveness of this combination in reducing gastric inflammation and pain.

65. Comment and testimony on OTC antacid drugs were presented June 6, 1973 before the Subcommittee on Monopoly of the Senate Select Committee on Small Business. It was reported by one physician that, during an 18-month period, he observed 18 patients in whom gastrointestinal hemorrhage was engendered by ingestion of aspirin preparations. In 5 patients, the preparation used was an effervescent antacid-analgesic product repeatedly taken over a short period of time to treat symptoms of gastric distress. Only one of the five patients referred to had no history of heavy alcohol ingestion, ulcer, or other serious disease that could well have caused the difficulty, prior to the ingestion of the combination. No controlled data were presented. The witness concluded that the advertising of the product as beneficial for stomach distress should cease, but acknowledged that it could be promoted as an analgesic. Another physician witness testified that many people are not aware of the potential hazards of salicylates or the true nature of their gastrointestinal symptoms, and questioned the advisability of including aspirin in any OTC drug preparations. The other witnesses presented their personal opinions as to the use of combinations but gave no data.

Based on the review of all the data submitted, the Commissioner concurs with the Panel that there is a significant target population having both symptoms. Even the witness describing the five patients had one patient taking an antacid and aspirin separately. The data submitted show the antacid-analgesic combination to cause less occult blood loss than taking each separately and there are no studies to indicate such a combination is not safe. One case history is not sufficient to demonstrate a lack of safety. If additional data are provided to show that the combination does cause more gastrointestinal hemorrhage than each taken separately and that the proposed labeling is insufficient to protect the public, then the Commissioner will reconsider the issue.

66. There was criticism of a study on an effervescent antacid-analgesic product contained in an unpublished 1968 report submitted by the manufacturer during the comment period and not previously available to the panel. The report describes a study performed in Australia by a physician in which the effect of the drug on gastrointestinal bleeding was evaluated in 20 subjects free of any gastrointestinal symptoms or disease. During oral testimony before the OTC Analgesic Panel meeting on July 30, 1973, the manufacturer stated that the report had not been submitted to the OTC Antacid Panel because of differences between the formulation marketed in Australia used in the study, and the formulation marketed in the United States. In the study, bleeding was estimated by fecal determination of radioactive chromium (CR^{51}) labeled red blood cells. The effects were measured for 16 consecutive days on each subject—8 days with treatment (2 tablets 4 times daily) and 8 days without treatment (control period). Employing statistical procedures, the investigator omitted the values of three subjects having blood loss well in excess of the range of the other subjects. He concluded that the drug produced no significant blood loss. One comment, using a different statistical approach which included the aberrant values, found a statistically significant increase in bleeding for each subject. Further evaluation by others using additional statistical methods are conflicting. Previous data submitted to the Panel included six other fecal blood loss studies, in addition to the Australian study. All investigators concluded that there was no significant blood loss from the product.

The Commissioner concludes that the findings in the Australian study are not consistent with blood loss patterns normally observed following ingestion of aspirin. Three subjects had blood loss in excess of the range of other subjects on one day during drug treatment, but were essentially normal within 24 hours. Only one subject for three consecutive days had excessive blood loss during the treatment period but showed marked improvement with no blood loss on the final day of the study. If the blood loss were attributable to the product, it should have continued for the duration of the treatment period.

The Commissioner further concludes, on reviewing all the blood loss studies and other available data, that the blood loss reported in the Australian study is not clinically significant. Normal blood loss often exceeds the relatively small amount lost by even the three high subjects. Nor is there evidence to show that

a small increase in blood loss is in any way harmful to persons taking OTC medications, particularly since the choice is between taking the analgesic and antacid separately or in combination.

67. There was comment that the Panel should have found simethicone to be a safe and effective antiflatulent. The comment stated that, in failing to do so, the Panel had reached a conclusion which was inconsistent with § 130.301(a)(4)(ii), because the Panel accepted the fact that simethicone was effective for lessening postoperative gas pains and amounts of gaseous accumulations as judged by x-ray. Using the definition of effectiveness the comment found that there is a reasonable expectation that a significant portion of the target population will obtain clinically significant relief of the type claimed.

The Commissioner, after reviewing the panel report and the additional data submitted (see paragraph 68), concludes that simethicone is a safe and effective antiflatulent. However, because this ingredient is not an antacid the Commissioner has concluded to establish a separate monograph for antiflatulents. He also recognizes the possibility that other safe and effective antiflatulents may be available but were not submitted to the Antacid Panel. For this reason, he has decided that any other claimed antiflatulent active ingredients should be submitted when the call for data for miscellaneous internal products is published. After such data are reviewed, the Commissioner will amend the antiflatulent monograph to include any additional safe and effective ingredients.

68. There were comments that antacid-simethicone combinations should have been found to be a safe and effective antacid-antiflatulent, because excessive gas and bloating generally accompany functional gastrointestinal disturbances. It was stated that the consumer may not be able to distinguish between symptoms caused by gastric acid and those caused by gas accumulation and that the combination of an antacid and simethicone is useful in both types of distress without decreasing the safety or efficacy of either ingredient. The Panel had questioned whether coalescence of gas bubbles is clinically beneficial, whether simethicone reduces gas accumulation symptoms under ordinary conditions of life, and whether any of the sensations of gas accumulation are actually produced by the gas. Two additional studies evaluating simethicone alone were submitted during the comment period in an attempt to resolve these questions: (1) A double blind 10-day study in which patients evaluated the reduction of gas accumulation symptoms, and (2) a double blind cross-over study evaluating symptoms after ingestion of a symptom-provoking meal. In both studies, the patients showed a statistically significant preference for simethicone over the placebo.

After reviewing the Panel report, the data filed in the original submissions and the two additional studies, the Commissioner had determined there is a reasonable expectation that simethicone will be effective if used in such a combination. Proper labeling of the combination is important. Any claim of effectiveness for an antacid-simethicone combination must be related to the antacid properties of the product because there is a lack of evidence that the combination is effective for gas accumulations alone. The tentative final monograph for antacids has been amended to include an antacid-antiflatulent combination, and a separate antiflatulent monograph has been established.

INACTIVE INGREDIENTS

69. There was comment that the maximum dosage of lactose is unreasonable because § 130.305(a)(9) allows milk solids to be used without limitation and dairy products are often used in a Sippy regimen.

The Panel's primary concern was for those individuals unable to produce sufficient lactase enzyme to digest lactose. These lactase deficient individuals normally limit their consumption of milk products which contain lactose.

The comment is correct. The limitation is inconsistent and will be revised. The Commissioner has concluded that lactase deficient individuals should be provided with the labeling information and a statement has therefore been added to the warnings, § 130.305(c).

COMMISSIONER'S DETERMINATION OF (CATEGORY II) CONDITIONS UNDER WHICH ANTACID PRODUCTS ARE NOT GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE OR ARE MISBRANDED

Based upon the record before him (all data submitted, the minutes of the Panel meetings, the Panel report, and all comments), the Commissioner determines that the use of antacids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Commissioner concludes that the ingredients, labeling, and combination drugs involved should not be permitted in interstate commerce effective as of 6 months after publication of the final monograph in the FEDERAL REGISTER, until scientific testing supports their use.

A. *Active ingredients.* No active ingredients that are not included in the Monograph or Category III have, in the Commissioner's opinion, been shown by adequate and reliable scientific evidence to be safe and effective.

B. *Labeling.* The Commissioner concludes that it is not truthful and accurate to make claims or to use indications on the package label that the product may directly affect "nervous or emotional disturbances." "excessive smoking," "food intolerance," consumption of "alcoholic beverages," "acidosis," "nervous tension headaches," "cold symptoms," and "morning sickness of pregnancy" since the relationship of such phenomena to gastric acidity is both unproven and unlikely.

C. *Drugs combining antacid and other active ingredients.* 1. The Commissioner concludes that it is valid to combine an antacid with aspirin for the purpose of buffering the aspirin and for the treatment of concurrent symptoms. He further concludes that fixed antacid-aspirin combinations are irrational for antacid use alone and therefore may not be labeled or marketed for such use. Not only are OTC antacids sometimes indiscriminately used, which may lead to aspirin toxicity with such combinations, but aspirin also has a potential for damaging the gastrointestinal mucosa by the topical action of breaking the mucosal barrier or by other mechanisms. Because of this potential and the lack of evidence of effectiveness of salicylate for antacid indications, benefit-risk considerations dictate that such a product not be indicated solely for antacid purposes.

2. The Commissioner concludes that it is not safe and effective concurrent therapy to add an anticholinergic ingredient to an OTC antacid product, because optimal use of antacids and anticholinergic drugs requires independent adjustment of dosages of each drug, because the addition of an anticholinergic drug in a concentration large enough to have detectable pharmacologic effects would result in a compound too toxic for use in self-medication, and because entirely safe amounts of anticholinergics have not been shown to affect gastric secretion or upper gastrointestinal symptoms. Since elderly persons number prominently among antacid users, cycloplegia and urinary retention induced by anticholinergic drugs is a definite risk. Thus, a fixed combination of antacid and anticholinergic will result, regardless of how formulated, in a mixture that is either unsafe or ineffective.

For the same reasons, the Commissioner also concludes that it is not safe and effective concurrent therapy to combine antacids with sedative-hypnotic ingredients.

3. The Commissioner concludes that it is not rational concurrent therapy for a significant portion of the target population for the label to claim that a combination product (e.g., mineral oil and magnesium hydroxide) is to be used both as an antacid and as a laxative if the laxative claim is supported by a non-antacid laxative ingredient.

The Commissioner recognized that there are active antacid ingredients to be reviewed by the OTC Laxative Panel that may be effective as laxatives at higher doses than those used for antacid action, and for this reason takes no position on use of these ingredients as laxatives at this time.

4. The Commissioner is not aware of any study showing that the addition of an antipeptic agent to an antacid product increases the product's efficacy as an antacid or is otherwise effective as a means of managing upper gastrointestinal symptoms. All antacids are antipeptic in the sense that peptic activity is reduced as pH increases and pepsin is irreversibly inactivated at pH's above 7. No claim for antipeptic activity can be considered

truthful and accurate until it is substantiated both by scientifically valid in vitro tests showing that the antipeptic action is substantially greater than that of an agent with only antacid action (such as sodium bicarbonate), and it is proved by studies that the antipeptic activity is clinically meaningful and therefore contributes significantly to the product's effectiveness.

5. The Commissioner concludes that the addition of proteolytic agents or bile or bile salts to antacid products is unsafe. Since pepsin is presumably involved in the pathogenesis of peptic ulcer, the addition of pepsin to antacid products may be potentially harmful. Since bile and bile salts can damage gastric mucosa, and since they may be involved in the pathogenesis of gastric ulcer, these substances should not be permitted in antacid products.

6. The Commissioner concludes that the addition of an antiemetic to an antacid product is not rational therapy for a significant portion of the target population.

COMMISSIONER'S DETERMINATION OF (CATEGORY III) CONDITIONS FOR WHICH THE AVAILABLE DATA ARE INSUFFICIENT TO PERMIT FINAL CLASSIFICATION AT THIS TIME

Based upon the record before him, the Commissioner determines that adequate and reliable scientific evidence is not available at this time to permit final classification of the active ingredients listed below.

A. *Active ingredients.* These ingredients have either no or negligible antacid action, and there is inadequate evidence of their effectiveness for their nonantacid action in the relief of upper gastrointestinal symptoms or in their adjuvant or corrective properties. The Commissioner concludes it reasonable to provide 2 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken to prove effectiveness, provided that any product that claims to be an antacid (i.e., neutralize stomach acid) meets the in vitro antacid effectiveness standard (see monograph). If adequate effectiveness data are not obtained within 2 years, these ingredients listed in this category should no longer be permitted, even in a product that meets the in vitro antacid effectiveness standard, because of a lack of evidence that these ingredients make a meaningful contribution to the claimed effects.

1. *Alginic acid.* Although the ingestion of alginic acid-containing products may produce a layer of material floating on top of the gastric contents, the Commissioner concludes that present evidence is insufficient to demonstrate the effectiveness of this action. The studies are fragmentary, uncontrolled, and few in number. No evidence is presented as to reproducibility of results. There is insufficient evidence that alginic acid-containing antacid products, even if they do produce a floating layer on top of the gastric contents, are clinically beneficial. Indeed, such evidence as there is indicates that these products do not increase the pH of gastric contents as a whole. Since regurgitation of gastric contents is particularly apt to occur when patients are lying down rather than in the upright position, alginic acid-containing products may be less beneficial than a standard antacid which is more likely to increase the pH throughout the gastric contents.

The Commissioner concludes alginic acid to be safe in amounts usually taken orally (e.g., 4 grams per day) in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

2. *Attapulgite (activated).* The Commissioner concludes that this ingredient is safe in the amounts usually taken orally in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

3. *Charcoal, activated.* The Commissioner concludes charcoal to be safe in amounts usually taken orally in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time. Since charcoal-containing products may decrease absorption of certain oral drugs, the label should state during this interim period the standard drug interaction warning: "Warning: Do not take this product concurrently with a prescription drug except on the advice of your physician." Study is specifically needed to determine whether the charcoal used contains benzpyrene or methylcholanthrane type carcinogens.

4. *Gastric mucin.* The Commissioner concludes that this ingredient is safe in the amounts usually taken orally in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

5. *Kaolin.* The Commissioner concludes kaolin to be safe in amounts usually taken orally in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

Since kaolin affects gastrointestinal absorption, the Commissioner concludes that ethical labeling should indicate that kaolin may interfere with the absorption of other drugs.

6. *Methylcellulose.* The Commissioner concludes methylcellulose to be safe in amounts usually taken orally (e.g., 2 grams per day in antacid products), and believes it unnecessary to impose a specific dosage limitation at this time.

7. *Pectin.* The Commissioner concludes that this ingredient is safe in the amounts usually taken orally in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

8. *Carboxy methylcellulose.* The Commissioner concludes carboxy methylcellulose to be safe in amounts usually taken (e.g., 3 grams per day) in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

B. *Labeling.* 1. OTC products containing ingredients listed in Category I or III are often used to treat symptoms that are not known to be related to acidity of gastric contents. These products may or may not qualify as antacids by the in vitro acid neutralizing test. The symptoms include "indigestion," "gas," "upper abdominal pressure," "full feeling," "nausea," "excessive eructations," "upset stomach," and the like. Some of these symptoms are vague, most are poorly understood as to pathophysiological mechanism, and none have been shown by adequate and reliable scientific evidence to be caused by or alleviated by changes in gastric acidity. The Commissioner concludes that companies marketing products that make claims for alleviation of these or other similar symptoms must within 2 years provide evidence of effectiveness, consisting of statistically valid clinical trials, in relieving each of these symptoms for which a claim is made. No claim for acid neutralizing properties can be made unless the product meets the in vitro standard (see monograph). Claims for those symptoms for which such evidence has not been provided by that time must be withdrawn.

2. The Commissioner concludes that claims or indications which link certain signs and symptoms, such as "sour breath," "upper abdominal pressure," "full feeling," "nausea," "stomach distress," "indigestion," "upset stomach," and "excessive eructations" with normal or hypernormal gastric acidity, are unproven since the relationship of such signs and symptoms to gastric acidity is unknown or dubious and there is no adequate and reliable scientific evidence to support these claims. Such claims or indications encourage the user to draw conclusions as to the cause or intermediation of such symptoms, a conclusion that even the medical professional is incapable of drawing at this time. Therefore, the Commissioner concludes those claims and indications that link these symptoms to acidity or "hyperacidity" should not be permitted unless supported by statistically valid clinical trials obtained within two years.

3. The Commissioner concludes that the evidence currently available is inadequate to support the claim that such properties as "floating," "coating," "defoaming," "demulcent," and "carminative" contribute to the relief of upper gastrointestinal symptoms. The continued use of such claims, or ones closely allied to them, requires additional studies both to confirm the claimed specific action and to demonstrate clinical significance. These studies must also be completed within two years.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 371), the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended; (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs is publishing as tentative final monographs new §§ 130.305 and

130.306, as amendments to Subpart D of Part 130, to read as follows:

§ 130.305 Antacids.

An over-the-counter antacid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 130.302.

(a) *Antacid active ingredient(s).* The active antacid ingredient(s) of the product consist(s) of one or more of the ingredients permitted in subparagraphs (2) through (14) of this paragraph within any maximum daily dosage limit established, each ingredient is included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product, and the finished product has a pH of 3.5 or greater at the end of the initial 10-minute period as measured by the method established in subparagraph (1) of this paragraph. To meet the 25 percent requirement, four times the amount of each ingredient present in a unit dose of a product containing two or more ingredients must meet the requirements of the acid neutralizing test. This requirement does not apply to an antacid ingredient specifically added as a corrective to prevent a laxative or constipating effect.

(1) The neutralizing capacity of the product shall be measured in the following way:

(i) Materials.

(*a*) Antacid.

(*b*) 0.1 N HCl.

(*c*) 1.0 N HCl.

(*d*) Standardizing buffer pH 4.0 (0.05 M potassium hydrogen phthalate).

(*e*) pH meter.

(*f*) Magnetic stirrer.

(*g*) Magnetic stirring bars (25 mm. long, 9 mm. diameter).

(*h*) 100 ml. beakers (45 mm. inside diameter).

(*i*) 50 ml. buret.

(*j*) Buret stand.

(*k*) 50 ml. pipet calibrated to deliver.

(*l*) Tablet comminuting device.

(*m*) Temperature controlling equipment.

(*n*) 12 and 16 standard mesh sieves.

(*o*) Phototachometer or similar device.

(ii) Procedure.

(*a*) Control temperature at 37° C.

(*b*) Standardize pH meter at pH 4.0 with standardizing buffer and at pH 1.1 with 0.1 N HCl.

(*c*) Place empty beaker on stirrer, add stirring bar, determine setting for stirring at 500 r.p.m. throughout.

(*d*) Add one unit dose of antacid and 50 ml. 0.1 N HCl to beaker. Acid or antacid may be added first. If antacid is in tablet form, it may be added as whole tablets or as particles except that if label states that tablets are to be swallowed whole, whole tablets should be used in the test. Particles should be prepared from ground tablets taking particles that pass a 12 standard mesh sieve and are held by a 16 standard mesh sieve. If particles are used, the weight of particles should equal the weight of a unit dose.

(*e*) Stir for exactly 10 minutes at 500 r.p.m.

(*f*) Read and record pH.

(*g*) If pH is 3.5 or greater, proceed; if pH is below 3.5, stop test.

(*h*) If pH in item (*g*) of this subdivision is 3.5 or greater, add 0.1 N or 1.0 N HCl from buret to bring pH to 3.5. Continue to add 0.1 N or 1.0 N HCl at the rate required to hold pH at 3.5.

(*i*) Exactly 5 minutes after beginning addition of 0.1 N or 1.0 N HCl (15 minutes after mixing antacide and acid) read and record ml. of 0.1 N or 1.0 N HCl used.

(*j*) Calculation: 5 mEq. (in 50 ml. 0.1 N HCl used in 1st 10 min.) + mEq(s) (number of mls. 1.0 HCl or 0.1 times number of mls. of 0.1 N HCl) added during period 10 to 15 min. = mEq. acid neutralized in 15 min.

(iii) The formulation and/or mode of administration of certain products (e.g., in chewing gum form) may require modification of this in vitro test.

(2) Aluminum-containing active ingredients:

(i) Aluminum carbonate.

(ii) Aluminum hydroxide (or as aluminum hydroxide-hexitol stablized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).

(iii) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid.

(iv) Aluminum phosphate, maximum daily dosage limit 8 grams.

(v) Dihydroxyaluminum sodium carbonate.

(3) Bicarbonate-containing active ingredients: Bicarbonate ion, maximum daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.

(4) Bismuth-containing active ingredients:

(i) Bismuth aluminate.

(ii) Bismuth carbonate.

(iii) Bismuth subcarbonate.

(iv) Bismuth subgallate.

(v) Bismuth subnitrate.

(5) Calcium-containing active ingredients: Calcium, as carbonate or phosphate, maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).

(6) Citrate-containing active ingredients: Citrate ion, as citric acid or salt, maximum daily dosage limit 8 grams.

(7) Glycine (aminoacetic acid).

(8) Magnesium-containing active ingredients:

(i) Hydrate magnesium aluminate activated sulfate.

(ii) Magaldrate.

(iii) Magnesium aluminosilicates.

(iv) Magnesium carbonate.

(v) Magnesium glycinate.

(vi) Magnesium hydroxide.

(vii) Magnesium oxide.

(viii) Magnesium trisilicate.

(9) Milk solids, dried.

(10) Phosphate-containing active ingredients:

(i) Aluminum phosphate, maximum daily dosage limit 8 grams.

(ii) Mono or dibasic calcium salt, maximum daily dosage limit 2 grams.

(iii) Tricalcium phosphate, maximum daily dosage limit 24 grams.

(11) Potassium-containing active ingredients.

(12) Sodium-containing active ingredients:

(i) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation). The maximum daily dosage limit is 200 mEq. of sodium for persons up to 60 years old and 100 mEq. of sodium for persons 60 years or older; and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.

(13) Silicates:

(i) Magnesium aluminosilicates.

(ii) Magnesium trisilicate.

(14) Tartrate-containing active ingredients. Tartaric acid or its salts, maximum daily dosage limit 200 mEq. (15 grams) of tartrate.

(b) *Indications.* The labeling of the product represents or suggests the product as an "antacid," to alleviate the symptoms of "heartburn," "sour stomach," or "acid indigestion."

(c) *Warnings.* The labeling of the product contains the following warnings:

(1) "Do not take more than (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonfuls) in a 24-hour period, or use the maximum dosage of this product for more than 2 weeks, except under the advice and supervision of a physician."

(2) For products which cause constipation in 5 percent or more of persons who take the maximum recommended dosage: "May cause constipation."

(3) For products which cause laxation in 5 percent or more of persons who take the maximum recommended dosage: "May have laxative effect."

(4) For products containing more than 50 mEq. of magnesium in the recommended daily dosage: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(5) For products containing more than 5 mEq. sodium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you are on a sodium restricted diet."

(6) For products containing more than 25 mEq. potassium in the maximum recommended daily dose: "Do not use this product except under the advice and supervision of a physician if you have kidney disease."

(7) For products containing more than 5 gm per day lactose in a maximum daily dosage: "Do not use this product except under advice and supervision of a physician if you are allergic to milk or milk products."

(d) *Directions for use.* The labeling of the product contains the recommended dosage per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by "except under the advice and supervision of a physician."

(e) *Statement of sodium containing ingredients.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq. (5 mg) or higher.

(f) *Ethical labeling.* The labeling of the product provided to physicians (but not to the general public):

(1) Shall contain the neutralizing capacity of the product, as calculated in paragraph (a)(1)(ii)(*j*) of this section, expressed in terms of the dosage recommended per minimum time interval or, if the labeling recommends more than one dosage, in terms of the minimum dosage recommended per minimum time interval. The neutralizing capacity value reported in such labeling may not exceed ten percent of the determined lower limit. Such labeling may indicate the value at the time of manufacture and/or after a specified period of time. No product may be marketed with an acid neutralizing capacity below 5 mEq.

(2) Shall, if the product is an aluminum or kaolin-containing antacid, contain a warning that absorption of other drugs may be interfered with by the aluminum or kaolin in the product.

(3) May contain an indication for the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, and hiatal hernia.

(g) *Combination with nonantacid active ingredients.* (1) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient (see laxative monograph) to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(2) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s) (see analgesic monograph) if it is indicated for use solely for the concurrent symptoms involved (e.g., headache and acid indigestion).

(3) An antacid may contain any generally recognized as safe and effective antiflatulent ingredient (see antiflatulent monograph) if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

§ 130.306 Antiflatulent.

An over-the-counter antiflatulent product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 130.302.

(a) *Active ingredient(s).* Simethicone. Maximum daily dose 500 mg.

(b) *Indications.* The labeling of the product represents or suggests the product as an "antiflatulent" to alleviate the symptoms of gas.

(c) *Directions for use.* The labeling of the product contains the recommended dosage per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age group if appropriate, followed by "except under the advice and supervision of a physician."

(d) *Ethical labeling.* The labeling of the product provided to physicians (but not to the general public) may contain as additional indications postoperative gas pain.

(e) *Combination with non-antiflatulent active ingredient(s).* An antiflatulent may contain any generally recognized safe and effective antacid ingredient(s) (see antacid monograph) if it is indicated for use solely for the concurrent symptom of gas associated with heartburn, sour stomach or acid indigestion.

Interested persons may file written objections and request an oral hearing before the Commissioner regarding this proposal on or before December 12, 1973. Request for an oral hearing must specify points to be covered and time requested.

All objections and requests shall be addressed to the Hearing Clerk, Food and Drug Administration, Room 6–86, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Received objections and requests may be seen in the above office during working hours, Monday through Friday. Any scheduled oral hearing will be announced in the FEDERAL REGISTER.

Dated: November 2, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-23927 Filed 11-9-73;8:46 am]

[21 CFR Part 130]

OVER-THE-COUNTER DRUGS

Proposed Procedures Regarding Public Comment on Review Panel Reports

Section 130.301(a)(6) of the procedures governing the over-the-counter (OTC) drug review provides that, after an advisory review panel issues its report to the Commissioner of Food and Drugs, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing his proposed action.

In reviewing the report of the first OTC advisory review panel, on antacids, it became apparent to the Commissioner that it would be more expeditious to publish the panel's report and proposed monograph, without change, in order to obtain full public comment before he made any decision on the matters involved. It appears likely that this procedure may also be useful for handling the reports of other OTC advisory review panels. The Commissioner believes that this procedure is within the intent of the existing regulation, but comments on the proposed antacid monograph contended that it is not. Accordingly, to clarify this matter the Commissioner is proposing to revise § 130.301(a)(6) explicitly to incorporate this procedure.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243, as amended; (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes to amend 21 CFR 130.301(a)(6) by adding the following sentence to the end of the undesignated paragraph following subdivision (iv), to read as follows:

§ 130.301 Over-the-counter (OTC) drugs for human use; procedures for rulemaking for the classification of OTC drugs as generally recognized as safe and effective and not misbranded under prescribed, recommended, or suggested conditions of use.

* * * * *

(a) * * *

(6) * * *

(iv) * * *

* * * The Commissioner may satisfy this requirement by publishing in the FEDERAL REGISTER a proposed order summarizing the full report of the advisory review panel, containing its conclusions and recommendations, in order to obtain full public comment before undertaking his own evaluation and decision on the matters involved.

* * * * *

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before December 12, 1973. Comments should be filed with the Hearing Clerk, Food and Drug Administration, Room 6–86, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated November 2, 1973.

A. M. SCHMIDT,
Commissioner of Foods and Drugs.

[FR Doc.73-23926 Filed 11-9-73;8:46 am]