DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 130]

OVER-THE-COUNTER DRUGS

Proposed General Conditions for OTC Drugs Listed as Generally Recognized as Safe and Effective and as Not Misbranded

In the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), the Commissioner of Food and Drugs established procedures for classification of over-the-counter (OTC) drugs under subpart D of part 130 (21 CFR part 130). The Commissioner is publishing in this issue of the FEDERAL REGISTER the first proposed monograph (21 CFR 130.305) under those new procedures. The monograph is proposed for OTC antacid products.

In considering this first monograph, the Commissioner has concluded that there are several general conditions applicable to all OTC drugs that are more appropriately established through a single regulation, rather than repeated in each monograph. The Commissioner therefore proposes to establish these general conditions, which will be applicable to every OTC drug subject to a monograph established under subpart D of part 130.

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 part 130 by adding a new § 130.302 to read as follows:

§ 130.302 General conditions.

An over-the-counter (OTC) drug listed in this subpart is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this section and each of the conditions contained in an applicable monograph. Any product which fails to conform to each of the conditions contained in this section and in an applicable monograph is liable to regulatory action.

(a) The product is manufactured in compliance with current good manufacturing practices, as established by Part 133 of this chapter.

(b) The establishment(s) in which the drug product is manufactured is registered, and the drug product is listed, in compliance with Part 132 of this chapter. It is requested but not required that the number assigned to the product pursuant to Part 132 of this chapter appear on all drug labels and in all drug labeling. If this number is used, it shall be placed in the manner set forth in Part 132 of this chapter.

(c) The product is labeled in compliance with Chapter V of the act and § 1.100 et seq. of this chapter. For purposes of § 1.102a(b) of this chapter, the statement of identity of the product shall be the term or phrase used in the applicable monograph established in this subpart.

(d) The advertising for the product prescribes recommends, or suggests its use only under the conditions stated in the labeling.

(e) The product contains only safe and suitable inactive ingredients which are harmless in the amounts administered and do not interfere with the effectiveness of the preparation or with prescribes, recommends, or suggests its tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 706 of the act and Parts 8 and 9 of this chapter.

(f) The product is packed in a container that is suitable and not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the product.

(g) The labeling contains the general warning: "Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a physician immediately." The Food and Drug Administration will grant an exemption from this general warning where appropriate upon petition.

(h) Where no maximum daily dosage limit for an active ingredient is established in this subpart, it is used in a product at a level that does not exceed the amount reasonably required to achieve its intended effect.

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before June 4, 1973. Such comments should be addressed to the Hearing Clerk, Department of Health, Education, and Welfare, Food and Drug Administration, Room 6–88, 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: March 9, 1973.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc.73-5656 Filed 4-4-73;8:45 am]

[21 CFR Part 130]

OVER-THE-COUNTER DRUGS

Proposal Establishing a Monograph for OTC Antacid Products

Pursuant to 21 CFR Part 130, the Commissioner of Food and Drugs received on January 23, 1973, the report of the Advisory Review Panel on over-the-counter (OTC) antacid drugs. In accordance with § 130.301(a)(6), the Commissioner is publishing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC antacid drugs are generally recognized as safe and effective and not misbranded, (2) a statement of the conditions excluded from the monograph on the basis of determination by the Panel that th would result in the drugs not being ge erally recognized as safe and effective o would result in misbranding, (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above, and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are available upon request from the Hearing Clerk of the Food and Drug Administration.

The Commissioner has not yet evaluated the report, and has not considered whether any clarification or modification of its recommendations may be appropriate for regulatory purposes. The Commissioner has concluded that the recommendations of the Panel report should be issued immediately as a formal proposal, in order to obtain full public comment, before any decision is made on these matters.

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 have been handled by the Panel and the Food and Drug Administration as confidential. All such data and information shall be put on public display at the Office of the Hearing Clerk of the Food and Drug Administration on May 7, 1973, except to the extent that the person submitting it demonstrates that it still falls withi the confidentiality provisions of 18 U.S. 1905 or 21 U.S.C. 331(j). Requests f confidentiality shall be submitted to the Food and Drug Administration, Bureau of Drugs, OTC Drug Products Evaluation Staff (BD–109), 5600 Fishers Lane, Rockville, Md. 20852.

The Panel did not propose a specific effective date for implementation of the monograph. In view of the fact that the procedure for OTC drug review gives the affected industry substantial advance warning of the likely impact of the final regulation, thus providing ample time for both reformulation and labeling changes long before issuance of a final regulation, the Commissioner proposes to establish an effective date of the final regulation that is 6 months after its publication in the FEDERAL REGISTER. In the event the specific issues relating to particular products are not finally resolved until promulgation of the final regulation, the Commissioner will grant individual exceptions to this effective date, based upon a petition showing hardship.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions excluded from the monograph on the basis of the Panel determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding, as set out in the Panel's recommendations, be eliminated from

OTC drug products effective 6 months ... publication of the final monograph ...EDERAL REGISTER, regardless whether ...her testing is undertaken to justify their future use.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded, or as not being generally recognized as safe and effective or would result in misbranding, as set out in the Panel's recommendations, be permitted to remain in use until 2 years after the effective date of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

The conclusions and recommendations submitted to the Commissioner of Food and Drugs by the Panel are as follows:

In the FEDERAL REGISTER for January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness, and labeling of all over-the-counter (OTC) drugs by independent advisory review panels. The same day the Commissioner published a request for data and information on all active ingredients utilized in antacid products (37 FR 102).

On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review (37 FR 9464), ...ich were made effective immediately. ... additional 30 days were allowed in ...e preamble to those final regulations for interested parties to submit data on antacid drugs.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC antacid products pursuant to the requirements of the regulations:

Franz J. Ingelfinger, M.D., Chairman	Edward W. Moore, M.D.
Howard C. Ansel, Ph. D.	John F. Morrissey, M.D.
Morton I. Grossman, M.D.	Howard M. Spiro, M.D.
Stewart C. Harvey, Ph. D.	

The Panel was first convened on February 22, 1972, in an organizational meeting. Five working meetings were held, on May 8, June 21, 22, and 23, August 10, 11, and 12, September 7, 8, and 9, and December 8 and 9.

Two nonvoting liaison representatives, Ms. Annette Dickinson, named by an ad hoc group of consumer organizations, and Joseph M. Pisani, M.D., nominated by the Proprietary Association, participated in all Panel discussions. Serving as executive secretary were Gladys Rosenstein, M.D., and acting in her absence, Armond M. Welch, both employees of the Food and Drug Administration.

In addition to the Panel members and liaison representatives, the Panel utilized the advice of four consultants:

P. M. Berman, M.D.	A. S. Relman, M.D.
J. B. Kirsner, M.D.	J. S. Fordtran, M.D.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or the Panel's request:

G. Beckloff, M.D.	J. Krantz, Ph. D.
B. Brennan, Esq.	J. Lamar, Ph. D.
R. Bregle, Ph. D.	T. Macek, Ph. D.
D. Carter, M.D.	H. Miller, M.D.
A. Cooke, M.D.	B. Misek, Ph. D.
T. Fand, Ph. D.	C. Pitkin, R. Ph.
W. Feinstone, Sc. D.	A. Ringuette, Esq.
A. Flanagan, M.D.	G. Sunshine, Esq.
D. Johnson, Esq.	G. Swenson, Esq.
K. Kimura, M.D.	

No other person requested an opportunity to appear before the Panel.

SUBMISSION OF DATA AND INFORMATION

Pursuant to the two notices published in the FEDERAL REGISTER requesting the submission of data and information on antacid drugs, the following firms made submissions relating to the indicated products:

Firm	*Product*
A. H. Robins Co., Richmond, Va. 23220.	Robalate.
	Silain.
American Cyanamid Co., Princeton, N.J. 08540.	Aciban.
Ayerst Laboratories, New York, N.Y. 10017.	Riopan.
Beecham, South Clifton, N.J. 07012.	ENO.
Bernhoft Laboratories, Bremerton, Wash. 98310.	Glycinate Tablets.
Boericke & Tafel, Inc., Philadelphia, Pa. 19107.	Anti-Acid.
	Carbo Pancreatin Pepsin Combination Tablets.
Bowman, Canton, Ohio 44702.	Antacid Tablets No. 2, Special.
	Bowcid.
	Digastrogen.
	Magnesil w/cal. carb.
	Milk of Magnesia, USP.
	Soda Mint—5 gr.
	Sodium Bicorbanate—5 gr.
E. D. Bullard Co., Sausalito, Calif. 94965.	Digestive Compound.
	Digestive Mixture.
C. S. Dent & Co., Cincinnati, Ohio 45202.	Bell-ans.
Chattem Laboratories, Chattanooga, Tenn. 37409.	Dihydroxaluminum Aminoacetate.
	Dihydroxaluminum Sodium Car.
Church & Dwight Co., Inc., New York, N.Y. 13201.	Sodium Bicarbonate.
E. R. Squibb & Sons, Inc., Princeton, N.J. 08540.	Milk of Magnesia.
Faraday Labs., Inc., Hillside, N.J. 07205.	Antacid Tablets.
	Gel-Us-Drug Formula.
Forest Labs., Inc., New York, N.Y. 10022.	Muco-25
	Mucogel-OC
Fugi Chemical Industry Co., Ltd., Tokyo, Japan.	Neusilin A/Neusilin B
G. M. Case Laboratories, San Diego, Calif. 92103.	Antacid Tablets.
	Flik Tablets.
Garfield & Co., Edison, N.J. 08817.	Seidlitz Powders.
Henry Labs., Inc., Pasco, Wash. 99301.	Formula 1447.
HLH Products, Dallas, Tex. 75207.	HLH Amaze Aids.
Humphreys Pharmacal, Inc., Rutherford, N.J. 07070.	Papsomax.
ICI America, Inc., Wilmington, Del. 19899.	Mylanta.
	Mylanta II.
Illinois Herb Co., Chicago, Ill. 60651.	Mucelo.
	Pectalo.
Jenkins Labs., Inc., Auburn, N.Y. 13021.	Antacid Special No. 1.
	Calicarb No. 1.
	Carbotabs.
	Hykaloid.
	Kaocasil.
	Sodium Bicarbonate.
Kremers-Urban Co., Milwaukee, Wis. 53201.	Kudrox.
Lewis-Howe, Co., St. Louis, Mo. 63102.	Dicarbosil.
	Milk of Magnesia.
	Tums.
Mallinckrodt Pharmaceuticals, St. Louis, Mo. 63160.	Krem.
Marion Labs., Inc., Kansas City, Mo. 64137.	Gaviscon.
McKesson Laboratories, Bridgeport, Conn. 06602.	Kessadrox.
	Magnex.
	Milk of Magnesia.
	Sodium Bicarbonate.
Medical Chemicals Corp., Melrose Park, Ill. 60160.	Medalox.
	Medicil.
Merrell-National Labs., Cincinnati, Ohio 45215.	Delcid.
	Kolantyl.
Miles Labs., Inc., Elkhart, Ind. 46514.	Alka-Seltzer.
	Alka-2.
Mitchum-Thayer, Inc., Paris, Tenn. 38242.	Amitone.
Philips Roxane Laboratories, Columbus, Ohio 43216.	Aluminum Hydroxide Gel.
	Antacid No. 4.
	Magnesia and Alumina Oral Susp: USP.
	Milk of Magnesia, USP.
Plough, Inc., Memphis, Tenn. 38101.	Chooz.
	Di-Gel.
Reid-Provident Labs., Inc., Atlanta, Ga. 30308.	Eugel Tabs and Suspension.
Riker Laboratories, Northbridge, Calif. 91324.	Titralac.
William H. Rorer, Inc., Fort Washington, Pa. 19034.	Camalox.
	Maalox.
Savoy Drug & Chemical Co., Michigan City, Ind. 46360.	Special Suspension.
	Special Tablets.
House of Schomburg, Fort Wayne, Ind. 46808.	Schomburg Powder.
Scott Labs. Inc., Corpus Christi, Tex. 78408.	Citrate of Magnesia.
Smith, Miller, & Patch, Inc., New Brunswick, N.J. 08902.	Alzinox (MAGMA).

Firm	Product
Sterling Drug, Inc., New York, N.Y. 10016.	Aluminum Hydroxide.
	Al-caroid.
	Calcium Carbonate.
	Creamalin.
	Fizrin.
	Haleys M-O.
	Magnesium Trisilicate.
	Mil-Par.
	Pepsamar.
	Phillips 203.
	Phillips Milk of Magnesia.
	Sal Andrews.
	Tricreamalate.
	Wingel.
T. R. Gibbs Medicine Co., Inc., Washington, D.C. 20020.	Push.
C. S. J. Tutag & Co., Detroit, Mich. 48234.	Escot.
Udga, Inc., St. Paul, Minn. 55114.	Udga Tablets.
The Upjohn Co., Kalamazoo, Mich. 49002.	Alkets.
	Anachloric A.
	Malcogel.
	Malcotabs.
Vick Chemical Co., New York, N.Y. 10017.	Vanamil.
Vitaminerals, Inc., Glendale, Calif. 91201.	VM-21 Gastric Antacid.
Warner-Chilcott Laboratories, Morris Plains, N.J. 07950.	Gelusil Flavor Pak.
	Gelusil-Lac.
	Gelusil Liquid.
	Gelusil-M-Liquid.
	Gelusil-M-Tablets.
	Gelusil Tabs.
	Mucotin.
Warner - Lambert Products Division, Morris Plains, N.J. 07950.	Bromo Seltzer.
	Rolaid Liquid.
	Rolaid Tablets.
Warren-Teed Pharmaceuticals, Inc., Columbus, Ohio 43215.	Ratio.
Whitehall Laboratories, New York, N.Y. 10017.	Bisodol.
Wyeth Laboratories, Philadelphia, Pa. 19101.	Aludrox.
	Aludroxetal.

The labeled active ingredients contained in these products are as follows:

Acetaminophen.
Alginic acid.
Aluminum carbonate.
Aluminum hydroxide.
Aluminum hydroxide—hexitol-stabilized polymer.
Aluminum hydroxide—magnesium carbonate, co-dried gel.
Aluminum hydroxide—magnesium trisilicate co-dried gel.
Aluminum hydroxide—sucrose powder—hydrated.
Aluminum phosphate.
Aspirin.
Atropine sulfate.
Attapulgite, activated.
Belladonna special extract (dry).
Bismuth aluminate.
Bismuth carbonate.
Bismuth subcarbonate.
Bismuth subgallate.
Bismuth subnitrate.
Caffeine.
Calcium carbonate.
Calcium phosphate.
Carboxy methylcellulose.
Cerium oxalate.
Charcoal.
Citric acid.
Dicyclomine.
Dihydroxyaluminum aminoacetate.
Dihydroxyaluminum aminoacetic acid.
Dihydroxyaluminum sodium carbonate.
Gastric mucin.
Ginger.
Glycine (aminoacetic acid).
Homatropine methylbromide.
Hydrated magnesium aluminate sulfate activated.
Kaolin.
Magaldrate.
Magnesium aluminosilicates.
Magnesium carbonate.
Magnesium glycinate.
Magnesium hydroxide.
Magnesium oxide.
Magnesium sulfate dihydrate.
Magnesium trisilicate.
Methylcellulose.
Milk solids dried.
Mineral oil.
Pancreatin.
Papain.
Pectin.
Pepsin.
Phenacetin.
Phenobarbital.
Potassium bromide.
Potassium citrate.
Powdered ipecac.
Rhubarb.
Salicylamide.
Simethicone.
Sodium bicarbonate.
Sodium carbonate.
Sodium potassium tartrate.
Tartaric acid.

The panel considered all pertinent data and information submitted in arriving at its conclusions and recommendations.

Active Ingredients. The Panel reviewed all active ingredients which were the subject of submissions made to the Panel pursuant to the standards for safety, effectiveness, and truthful labeling set out in the regulations.

In accordance with the regulations, the Panel's findings with respect to these ingredients are set out in three categories:

I. Conditions under which antacid products are generally recognized as safe and effective and are not misbranded.

II. Conditions under which antacid products are not generally recognized as safe and effective or are misbranded.

III. Conditions for which the available data are insufficient to permit final classification at this time.

I. *Conditions under which antacid products are generally recognized as safe and effective and are not misbranded.*

and effective and are not misbranded. A.

A. *Effectiveness standard.* OTC antacid products should be evaluated with respect to their acid neutralizing properties and neutralizing capacity by one set of criteria irrespective of whether these products are used to alleviate the symptoms of minor upper gastrointestinal complaints or major disorders such as peptic ulcer. OTC products marketed as antacids should be evaluated by the following standard in vitro test:

MEASUREMENT OF NEUTRALIZING CAPACITY OF ANTACIDS

MATERIALS

Antacid, 0.1 N HCl, 1.0 N HCl, standardizing buffer pH 4.0 (0.05 M potassium hydrogen phthalate), pH meter, magnetic stirrer, magnetic stirring bars (25 mm. long, 9 mm. diameter), 100 ml. beakers (45 mm. inside diameter), 50 ml. buret, buret stand, 50 ml. pipet calibrated to deliver, device for comminuting tablets, 12- and 16-mesh sieves, equipmen for controlling temperature.

PROCEDURE

1. The test should be conducted at 37° C.

2. Standardize the pH meter at pH 4.0 with standardizing buffer and at pH 1.1 with 0.1 N HCl.

3. Place empty 100 ml. beaker on stirrer, add stirring bar, center bar in beaker, adjust rotation rate to 240 r.p.m., record dial setting that produces this rotation rate. Turn off stirrer.

4. 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-mesh sieve and are held by a 16-mesh sieve. If particles are used, the weight of particles should equal the weight of a unit dose.

5. Immediately after adding acid and antacid, turn on stirrer to speed setting determined in step 3.

6. Stir for exactly 10 minutes.

7. Read and record pH.

8. If pH is 3.5 or greater, proceed; if pH is below 3.5, stop test.

9. If pH at Step 7 is 3.5 or greater, add 1.0 N HCl from buret to bring pH to 3.5. Continue to add 1.0 N HCl at the rate required to hold pH at 3.5.

10. Exactly 5 minutes after beginning addition of 1.0 N HCl (15 minutes after adding antacid) read and record ml of 1.0 N HCl used.

11. Calculation: 5 meq (in 50 ml 0.1 N HCl used in first 10 min) + number of ml 1.0 N HCl added during period 10 to 15 min = meq acid neutralized in 15 minutes.

Criterion 1: If pH is 3.5 or greater at end of initial 10-minute period, product may be labeled antacid.

Criterion 2: If antacid passes Criterion 1, neutralizing capacity as calculated in Step 11 must be stated in package insert of ethically promoted products. The neutralizing capacity should be expressed per unit dose recommended on the label, or per minimum unit dose if more than one dose is suggested.

The formulation and/or mode of administration of certain products (e.g., in chewing gum form) may require modification of this in vitro test. In vivo tests of antacid properties should not be required at this time.

Comment. The capacity to neutralize acid is one of the factors involved in the in vivo efficacy of antacids. In vitro tests such as the one proposed here can give an index of the magnitude of an ingredient's or product's capacity to neutralize acid. Other factors involved in in vivo efficacy, such as rate of gastric emptying, rate of secretion of acid by the stomach, and degree of mixing of antacid with gastric contents, are highly variable and cannot be usefully simulated in in

vitro tests. The proposed in vitro test ot purport to simulate these highly le factors and the panel does not ate more elaborate in vitro tests because it is not aware of any evidence showing that in vitro tests that attempt to simulate in vivo conditions give better predictions of in vivo efficacy than in vitro tests that measure only the acid neutralizing capacity of a product. The conditions of the proposed test were selected with the following considerations in mind.

Minimum acid neutralizing capacity of 5 mEq. The fasting stomach of patients with duodenal ulcer contains about 3 mEq. of acid at any given moment (residual content) and secretes about 0.13 mEq./min. or about 2 mEq. in 15 minutes. Control subjects have values about half those of duodenal ulcer subjects. Theoretical considerations predict and actual observations show that antacids are generally much less than 50 percent efficient in realizing in vivo their in vitro acid neutralizing properties. Therefore, for an antacid to combine with the residual gastric acid and to maintain an elevated pH for 15 minutes in a normal subject would require, on the average, 5 mEq. of antacid (assuming 50 percent efficiency).

pH endpoint of 3.5. A commonly used laboratory endpoint for antacids is pH 4, selected because peptic activity is reduced by more than 80 percent at this pH. Since many antacids in common use that are apparently effective in producing symptomatic relief have little buffer action at pH 4 (particularly aluminum containing compounds) the endpoint of pH 3.5 was selected. Further studies are needed to pinpoint the pH that must be achieved to produce relief of upper gastrointestinal symptoms that may be susceptible to relief by antacids.

Fifteen-minute duration of test. The rate of reaction of antacid with acid is not an index of duration of action in vivo. Specifically, a slow rate of in vivo elevation of pH will be prolonged. When an antacid is taken in the fasting state in ordinary doses, such as 15 ml. of a liquid preparation, the elevation of pH of gastric contents extends beyond 15 minutes in less than 40 percent of the subjects even when a preparation with high acid neutralizing capacity is used. This short duration of action is attributable to the rapid emptying of antacid from the stomach. Most of the antacid has left the stomach 15 minutes after ingestion, and therefore any acid neutralizing properties that take longer than 15 minutes to be manifest will not be effective.

The in vitro test specified is recommended as a means of introducing a reasonable, standardized procedure in what appears to be a chaotic situation at present. Modification of the test may be anticipated, perhaps after discussion and evaluation by an appropriate and widely representative committee of experts. Presently available in vivo tests themselves subject to multiple sources error and variability, so that no one of them can be designated as optimum. Therefore, in vivo tests are not recommended at this time since their routine implementation would require very laborious procedures without a commensurate increase in the information so obtained.

Although the application of an in vitro test as the sole standard of effectiveness for OTC antacids appears reasonable and practical for the moment, this single standard need not be perpetuated indefinitely. The Panel, therefore, recommends that the FDA organize an appropriate advisory group to develop within a reasonable period, such as 5 years, an in vivo standard of antacid effectiveness to be applicable, in addition to the in vitro test, to both OTC and prescription products.

CITATIONS

(1) Fordtran, J. S.: Morawski, S. G.: Richardson, C. T.; "Clinical Pharmacology of Antacid Therapy" (Draft of paper being submitted for publication).

(2) Grossman, M. I.; "Duration of Action of Antacids", American Journal of Digestive Diseases, *1*:453–454, 1956.

(3) Grossman, M. I.; Kirsner, J. B.; Gillespie, I. E.; "Basal and Histalog Stimulated Gastric Secretion in Control Subjects and in Patients With Peptic Ulcer or Gastric Cancer", Gastroenterology. *45*:14–26, 1963.

(4) Kronborg, O.; "An Evaluation of the Insulin Test", Fadls Forlag, Copenhagen, Denmark, 1972.

(5) Littman, A.; "Reactive and Nonreactive Aluminum Hydroxide Gels. Dose-response Relationships In Vivo", Gastroenterology, *52*:948–951, 1967.

(6) Myhill, J. and Piper, D. W.; "Antacid Therapy of Peptic Ulcer", Gut, *5*:581–589, 1964.

(7) Northrop, J. H.; Kunitz, M.; Herriott, R. M.; "Crystalline Enzymes"; 2d edition. Columbia University Press, New York, 1948.

B. *Active ingredients.* The Panel concludes that any ingredient listed in this category or products combining two or more such ingredients may be considered safe and effective provided that:

(a) The ingredient or product is recommended for use within the dosage level specified for its component moieties. When an ingredient or product contains two or more moieties for which maximum dosage levels have been specified, the smaller or smallest maximum dosage specified for the pertinent moieties should be applied to the ingredient or product.

(b) The product meets the requirements of the acid neutralizing test.

(c) Each ingredient, as determined by the acid neutralizing test, contributes at least 25 percent of the total neutralizing capacity of any product containing more than one ingredient. 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 stipulation need not apply to an antacid ingredient specifically added as a corrective to prevent a laxative or constipating effect.

Comment. Efficacy. Because the secretory activity of the stomach may vary extensively from person to person, and also from time to time in the same person, there is no rationale for setting a maximum limit to the intake of an OTC antacid on the basis of efficacy.

Safety. From the viewpoint of safety, maximum dosages are specified for a number of moieties. An excessive consumption of those moieties of an ingredient for which no maximum intake has been specified is unlikely because of the self-limiting factors exerted by bulk, palatability, or laxation.

The active ingredients with potential acid neutralizing properties are:

Aluminum carbonate.
Aluminum hydroxides.
Aluminum phosphate.
Bismuth aluminate.
Bismuth carbonate.
Bismuth subcarbonate.
Bismuth subgallate.
Bismuth subnitrate.
Calcium carbonate.
Calcium phosphate.
Citric acid (as citrate salt or generable citrate salt).
Dihydroxyaluminum aminoacetate.
Dihydroxyaluminum aminoacetic acid.
Dihydroxyaluminum sodium carbonate.
Glycine (aminoacetic acid).
Hydrated magnesium aluminate activated sulfate.
Magaldrate.
Magnesium aluminosilicates.
Magnesium carbonate.
Magnesium glycinate.
Magnesium hydroxide.
Magnesium oxide.
Magnesium trisilicate.
Milk solids, dried.
Sodium bicarbonate.
Sodium Carbonate.
Sodium potassium tartrate.
Tartaric acid (as tartrate salt or generable tartrate salt).

Comment.—In evaluating the active ingredients for inclusion into one of the three categories in this report, the Panel determined that the above active ingredients should be included in this category based on the evidence presently available. Additional scientific evidence is necessary to define with precision the use of many of these ingredients. Ideally, to support categorical statements of safety and efficacy, the kinds of data suggested in the appendix should be developed.

1. *Aluminum.* The Panel concludes aluminum to be safe in amounts usually taken orally in antacid products, and believes it unnecessary to impose a specific limitation at this time.

Comment. In man, less than 1 mg. aluminum per day appears in urine when aluminum hydroxide is taken. In experimental animals, huge doses of aluminum hydroxide raise the organ contents of aluminum only slightly. No animal toxicity has been observed after oral administration of aluminum, other than that attributable to the obstructive effects of the material ingested.

In man, the only reported adverse effects, intestinal obstruction by masses of aluminum hydroxide and blood, and bony abnormalities and other consequences of intraintestinal sequestration

of phosphate, are substantially infrequent and a warning is not necessary. In general, it appears that sequestration of phosphate by aluminum is a possible danger only if the patient is on a very low phosphate intake, has chronic diarrhea, or has an intrinsic disorder affecting calcium and/or phosphorus metabolism.

Aluminum compounds, it has been shown experimentally in man, interfere with the absorption of tetracycline, and, based on animal studies, they may theoretically interfere with the absorption of many other important drugs such as anticholinergics, barbiturates, warfarin, quinine, and its stereo isomer quinidine. The evidence, however, is fragmentary and conflicting. In addition, antacids other than aluminum compounds may also interfere with tetracycline absorption. Under these conditions, a warning on the label about possible interference with the absorption of prescription drugs is not justified at this time for OTC antacids. Ethical labeling, however, should indicate that aluminum-containing antacids may interfere with the absorption of other drugs.

CITATIONS

(1) Adams, W. L.; Einsel, I. H.; Myers, V. C.; "Aluminum Hydroxide As Antacid In Peptic Ulcer," American Journal Digestive Diseases and Nutrition, *3*:112–120, 1936.

(2) Barr, W. H.; Adir, M. S.; Garrettson, L.; "Decrease of Tetracycline Absorption in Man By Sodium Bicarbonate," Clinical Pharmacology and Therapeutics, *12*:779–784, 1971.

(3) Blaug, S. M. and Gross, M. R.; "In Vitro Absorption of Some Anticholinergic Drugs by Various Antacids," Journal Pharmaceutical Sciences, *54*:289–294, 1965.

(4) "Evaluation of Drug Interactions—1973," American Pharmaceutical Association. (To be published.)

(5) Hurwitz, A.; "The Effects of Antacids on Gastrointestinal Drug Absorption. II. Effect on Sulfadiazine and Quinine," Journal Pharmacology and Experimental Therapeutics, *179*:485–489, 1971.

(6) Hurwitz, A. and Sheehan, M. B.; "The Effects of Antacids on the Absorption of Orally Administered Pentobarbital in the Rat," Journal Pharmacology and Experimental Therapeutics, *179*:124–131, 1971.

(7) Robinson, D. S.; Benjamin, D. M.; McCormack, J. J.; "Interaction of Warfarin & Nonsystemic Gastrointestinal Drugs," Clinical Pharmacology and Therapeutics, *12*:491–495, 1971.

(8) Waisbren, B. A. and Hueckel, J. S.; "Reduced Absorption of Aureomycin Caused By Aluminum Hyroxide Gel," Proceedings of the Society for Experimental Biology and Medicine, *73*:73–74, 1950.

2. *Bicarbonate.* The Panel concludes that the maximum daily intake of bicarbonate ion in the form of an antacid should be 200 mEq/day for those under 60 years of age and 100 mEq/day for those older.

Comment. Alkalosis (i.e., increase in plasma pH outside the normal range) is not regarded by the Panel to be a danger at suggested maximum levels. Goidsenhoven found little change in plasma pH upon oral administration of large doses of sodium bicarbonate (up to 24 mEq/Kg/day for periods up to 3 weeks) although plasma bicarbonate levels tended to rise with increasing doses. Adequate data are not available on the effects of prolonged high bicarbonate intake. Relman found, in dogs, that respiratory compensation of metabolic alkalosis increases the renal bicarbonate threshold, tending to perpetuate the elevation of extracellular bicarbonate concentration. Pak-Poy and Wrong found that in certain patients with renal disease, bicarbonate excretion was reduced at given urine pH, suggesting that such patients may be more prone to alkalosis at given bicarbonate intake. The Panel and a consultant, A. S. Relman, believe that if the maximum daily dose is used for prolonged periods, alkalinity of the urine with urinary stone formation is a potential hazard.

CITATIONS

(1) Goidsenhoven, G. M. van; Gray, O. V.; Price, A. V.; Sanderson, P. H.; "The Effect of Prolonged Administration of Large Doses of Sodium Bicarbonate In Man," Clinical Science, *13*:383–401, 1954.

(2) Pak-Poy, R. K. and Wrong, O.; "The Urinary pCO_2 in Renal Disease," Clinical Science, *19*:631–639, 1960.

(3) Relman, A. S.; Etsten, B.; Schwartz, W. B.; "The Regulation of Renal Bicarbonate Reabsorption by Plasma Carbon Dioxide Tension," Journal of Clinical Investigation, *32*:972–978, 1953.

3. *Bismuth salts and subsalts.* The Panel concludes bismuth salts and subsalts marketed as antacids to be safe in amounts usually taken orally (e.g., 4 grams per day) and believes it unnecessary to impose a specific dosage limitation at this time.

Comment. The oral dose for adults of bismuth subcarbonate is given as 1 gram and the 4-gram amount is based on the assumption that the dose might be taken four times daily.

CITATION

(1) *AMA Drug Evaluations—1971,* 1st Edition, American Medical Association, Chicago, p. 580, 1971.

4. *Calcium.* The Panel recommends that not more than 160 meg of calcium (e.g., 8 grams of calcium carbonate) be taken per day. This recommendation is based on the fact that hypercalciuria in response to calcium ingestion is not rare in the population, and that hence the danger of renal stone formation has to be considered in determining the intake of calcium-containing antacids.

Comment. Calcium-containing antacids such as calcium carbonate stimulate gastric secretion in patients with peptic ulcer and probably in normal subjects. After single doses of such antacids, rates of acid secretion may reach levels of 2 to 4 times the basal rate and these elevations may persist for 1 to 2 hours, long after the antacid action has ended. The increase in acid secretion can at least in part be accounted for by elevation of plasma gastrin levels, but the increase is not clearly correlated with elevation of plasma levels of ionized calcium. The Panel knows of no studies of the effects of extended daily use (e.g., 1 week or longer) on the interrelationships of basal acid secretion, plasma ionized calcium concentration, and gastrin secretion. The Panel concludes that present information does not warrant a restriction on the use of calcium-containing antacids because of any possible stimulating effect on gastric secretion, but as more information becomes available such restrictions may prove to be advisable. Some experts at present believe that calcium-containing compounds should not be used as antacids.

CITATIONS

(1) Barreras, R. F.; "Acid Secretion After Calcium Carbonate In Patients With Duodenal Ulcers," New England Journal of Medicine, *282*:1402–1405, 1970.

(2) Barreras, R. F. and Donaldson, R. M., Jr.; "Effects of Induced Hypercalcemia on Human Gastric Secretion," Gastroenterology, *52*:670–675, 1967.

(3) Fordtran, J. S.; "Acid Rebound," New England Journal of Medicine, *229*: 900–905, 1968.

(4) Huth, E. J.; "The Kidney and Oral Calcium Therapy," Annals of Internal Medicine, *66*:1021–1022, 1967.

(5) Letters officially solicited by th Panel Chairman from experts in the field of calcium metabolism and excretion are included in the public file. These letters, including not only comments, but citations, are by J. E. Howard, L. J. Raisz, H. P. Schedl, G. D. Whedon, and R. E. Goldsmith.

(6) Reeder, D. D.; Conlee, J. L.; Thompson, J. C.; "Calcium Carbonate Antacid and Serum Gastrin Concentration in Duodenal Ulcers," Surgical Forum, *22*:308–310, 1971.

5. *Citrates.* The Panel concludes the citrate ion to be safe orally in amounts usually taken. The amount taken with antacids would probably be less than 8 grams per day. Since there is no reliable information as to the upper limits of a safe dose, this level is adopted as the maximum safe dosage at this time.

CITATION

(1) Sollmann, T.; "Manual of Pharmacology," 8th Edition; W. B. Saunders, Philadelphia, pp. 1186–1187, 1957.

6. *Glycine (aminoacetic acid).* The Panel concludes glycine to be safe in amounts usually taken orally (e.g., 5 grams per day) in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

Comment. Glycine is rapidly metabolized and is practically nontoxic, even with high blood levels produced by intravenous injections. Amino acids combine with acid but their buffering capacity is negligible above pH 2.5. Some

ar[illegible] acids stimulate gastric secretion [illegible]s stimulation may persist after t[illegible]ino acid has left the stomach. Ingestion of large amounts of individual amino acids or of imbalanced mixtures of amino acids can produce toxic effects in animals.

CITATIONS

(1) Collentine, G. E.; "On The Efficacy and Safety of Glycine Administered by Vein," Journal of Laboratory and Clinical Medicine, *33*:1555–1561, 1948.

(2) Cooke, A. R.; Moulang, J.; "Control of Gastric Emptying by Amino Acids," Gastroenterology, *62*:528–532, 1972.

(3) DiPalma, J. R.; "Drill's Pharmacology in Medicine," 3d Edition, McGraw-Hill, New York, p. 721, 1965.

(4) Harper, A. E.; Benevenga, N.J.; Wohlhueter, R. M.; "Effect of Ingestion of Disproportionate Amounts of Amino Acids", Physiological Reviews, *50*:428–558, 1970.

7. *Magnesium.* Absorption of magnesium from antacid preparations does not exceed 15–30 percent and is unlikely to cause systemic toxicity unless renal insufficiency is present. The Panel, therefore, concludes that based on the evidence it has at this time it is not necessary to restrict the intake of magnesium-containing antacids by normal persons because of possible systemic toxic effects of magnesium. For those products in which the maximal daily dose exceeds 50 mEq. of magnesium, the label should state: "Do not use this product if you h[illegible] kidney disease, except under the [illegible] and supervision of a physician." [illegible]ment. Approximately 20–40 mEq of magnesium are ingested in the normal adult daily diet. Approximately one-third of this amount is absorbed. From magnesium-containing antacids about 15 percent of the acid-reactive magnesium is absorbed, although absorption up to 30 percent has been reported. Absorbed magnesium rapidly enters the cells and is also rapidly excreted, so that hypermagnesmia is difficult to achieve by the oral route in the presence of normal renal function. In renal dysfunction, however, hypermagnesmia toxicity may occur and a warning is therefore necessary. Unabsorbed soluble magnesium compounds obligatorily retain water in the gut and exert a cathartic effect. However, the cathartic dose is higher than the dose recommended for magnesium-containing antacid products. Furthermore, not all of the magnesium compound may dissolve in the gut, and some preparations contain only small amounts of magnesium. In addition, constipating materials, such as calcium or aluminum, may be present. Consequently, many magnesium-containing antacid products may lack definite laxative action and not all products need carry a warning about laxation.

CITATIONS

(1) Goodman and Gillman; "The [illegible]macological Basis of Therapeutics," [illegible]dition, MacMillan Co., N.Y.; 813 [illegible]24, 1970.

(2) Letters solicited by the Panel Chairman from L. G. Welt and J. E. Howard are included in the public file.

(3) Randall, R. E. Jr.; Cohen, M. D.; Spray, C. C. Jr.; Rossmeisl, E. C.; "Hypermagnesemia in Renal Failure, Etiology and Toxic Manifestations," Annals of Internal Medicine, *61*:73–88, 1964.

8. *Milk, solids, dried.* The Panel concludes milk solids to be safe in amounts usually taken orally in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

9. *Phosphates.* The Panel concludes phosphates to be safe in amounts usually taken orally (e.g., 2 grams as the mono or dibasic calcium salt, 8.0 grams as aluminum phosphate, and 24 grams as tricalcium phosphate per day) in antacid products. No specific limitation is necessary with respect to safety at this time.

Comment. The above recommended levels are within the ranges found in the literature for various marketed products reviewed by the Panel; i.e., mono or dibasic calcium salt, 0.2 grams per tablet up to eight tablets per day; aluminum phosphate, up to 2 grams four times daily; tricalcium phosphate, 1 to 4 grams, up to six doses per day.

CITATION

(1) *AMA drug evaluations-1971,* 1st Edition, American Medical Association, p. 575, 1971.

10. *Potassium.* The Panel concludes that, with respect to normal persons, no evidence is available to warrant the imposition of a specific maximum daily intake of any antacid product on the basis of its potassium content. Patients with kidney disorders, however, should be warned not to take potassium-containing antacids: "Do not use this product if you have kidney disease except under the advice and supervision of a physician." This requirement does not apply to antacid products containing less than 25 mEq. of potassium per maximum daily dose.

Comment. Hyperkalemia as a consequence of oral ingestion of potassium is rare. As much as 30–60 meq per day of potassium is frequently given as a nutrient. A liter of orange juice contains about 50 meq of potassium. Meat contains about 65 meq of potassium per pound. Consequently, normal persons can easily tolerate the potassium content of currently marketed OTC antacid products. However, in the presence of impaired renal function, potassium can accumulate in the body and exert toxic effects, so the warning is in order.

11. *Silicates.* Although there are some definite reports of silicious renal stones, the Panel concludes that evidence at this time of frequent silicate toxicity is insufficient to justify a limit on the maximum daily intake of silicate in an antacid. Further studies on silicate toxicity are needed. Magnesium trisilicate is said to interfere with drug absorption, and the Panel questioned whether labeling should bear a statement concerning possible interference with the absorption of prescription drugs but concluded that the evidence was insufficient at this time to justify such a statement.

12. *Sodium.* The Panel concludes that the maximum safe daily dosage of sodium-containing antacids is 200 mEq of sodium for persons under 60 years of age, and 100 mEq for persons 60 years of age or older. The label on antacid products containing more than 5 mEq sodium per maximum recommended daily dose should state: "Do not use this product if you are on a sodium restricted diet except under the advice and supervision of a physician." All OTC antacids containing more than 0.2 mEq. (5 mg) of sodium in one unit dosage should show on the label the sodium content, expressed per tablet, per unit volume used for expressing dose, or per packet or packet combination.

Comment. There is extensive literature on the relationship of sodium intake to hypertension, and it is generally accepted that sodium intake is one of several factors in its pathophysiology. In experimental animals, salt may precipitate marked hypertension in the presence of certain endocrine and/or renal disturbances. Even in the absence of abnormalities, blood pressure increases with sodium intake. However, in the presence of normal renal function, the rise in pressure is moderate.

Guyton states that the doubling of salt and water intake raises the mean blood pressure in man by 10 mmHg. Prior and Evans studied a genetically homogeneous population scattered among three Polynesian islands. They concluded that diet and salt intake contributed to differences in blood pressure, but the relationship is complicated by other factors.

Apart from hypertension, edema may develop in persons with occult heart failure or renal disease with high salt intake. Since the prevalence of these conditions increases with age, it is advisable to place a more severe limit on sodium dosage for persons over 60 years of age.

Panel consultants concurred that sodium intake greater than 100 meq. per day might be deletrious in elderly patients or patients with cardiorenal disease. They also agreed that sodium intake up to 200 meq. per day would be safe in younger persons with normal cardiorenal status.

A limit of 200 meq. per day as antacid would allow additional sodium in medicinal form approximately equal to the usual daily intake in the American diet.

CITATIONS

(1) Letters solicited by the Panel chairman from William B. Schwartz and Edward Freis are included in the public file.

(2) Davies, D. F. and Shock, N. W.; "Age Changes In Glomerular Filtration Rate, Effective Renal Plasma Flow and Tubular Excretory Capacity In Adult Males," Journal Clinical Investigation, *29*:496–507, 1950.

(3) Guyton, A. C.; Coleman, T. G.; Fourcade, J. C.; Navar, L. G.; "Physiologic Control of Arterial Pressure," Bulletin of the New York Academy of Medicine, *45*:811–830, 1969.

(4) *"Handbook of Non-Prescription Drugs."* American Pharmaceutical Association, Washington, D.C., pp. 10–12, 1971.

(5) Lewis, W. H. and Alving, A. S.; "Changes With Age In The Renal Function In Adult Men," American Journal of Physiology, *123*:500–515, 1938.

(6) Prior, I. A. and Evans, J. G.; "Sodium Intake and Blood Pressure in Pacific Population," Israel Journal of Medical Science, *5*:608–611, 1969.

(7) Rimer, D. G. and Frankland, M.; "Sodium Content of Antacids," Journal of the American Medical Association, *173*:995–998, 1960.

(8) Shock, N. W.; "Kidney Function Tests in Aged Males," Geriatrics, *1*:232–239, 1946.

13. *Tartaric acid and tartrates.* The Panel concludes on the basis of the tartrate concentration of traditionally used agents, that the maximum daily dose of tartrates should be 200 meq (15 grams).

Comment. More information is needed concerning the overall influence of tartrates on the body. The diet contains variable amounts of tartaric acid and/or its salts sometimes in quantities exceeding those recommended in antacid therapy. Up to 1.2 percent in the diet of rats for 2 years caused no evident harm but 1.5 percent was toxic. In rabbits, no renal injury was seen up to 12 mmol/kg, but toxicity occurred at 17–25 mmol/kg. Long use of tartrates as cathartics and their use in baking powders seem to establish their safety. However, Robertson and Lonnel reported a death following the oral ingestion of 30 grams of tartaric acid. Renal failure with characteristic epithelial necrosis in the convoluted tubules and loop of Henle were observed. Krop and Gold reported chronic renal toxicity in dogs ingesting 0.99 gm per kg per day. The above cited doses are within the range of those conceivable with antacid preparations used repetitively throughout the day, day after day. Until tartrate-containing antacid preparations are carefully tested for toxicity, especially nephrotoxicity, under conditions simulating actual use and abuse, it is advisable to establish a daily dosage limit of 200 meq. It should be noted that the FAO/WHO Expert Committee on Food Additives in its eighth report recommended a conditional limit of 6–20 mg/kg/day (420–1400 mg per 70 kg per day) of tartaric acid.

Tartrate is a chelator of calcium, and its renal effects resemble those caused by other chelators. It has been reported to have a parathyroid hormone-like action. The cathartic effect (supposedly saline catharsis) and the studies in man by Underhill indicated poor oral absorption, yet no tartrate has been demonstrated in feces. Bauer and Pearson believe absorption is nearly complete and catabolism is the primary mode of elimination, in contradiction of the above cited workers. It is noteworthy that Post reported diuresis and alkalinization of the urine in man.

No study has been made by modern tracer or chromatographic methods. Whether tartrate is absorbed and excreted unchanged, metabolized to bicarbonate and excreted as bicarbonate, or converted to bicarbonate in the gut, then absorbed and excreted, a quantitative description of its effects on systemic acid-base physiology and the renal implications thereof are needed. Information about sodium potassium tartrate is needed to determine the bioavailability of both sodium and potassium and to establish its safety. Because of sodium-potassium exchange, potassium-calcium antagonism, the opposite effects of sodium and potassium on (Na-K) membrane ATPase, etc., findings with sodium tartrate cannot be considered to apply automatically to sodium potassium tartrate, and both tartrates should be studied separately.

CITATIONS

(1) Bauer, C. W. and Pearson, R. W.; "A Comparative Study of the Metabolism In the Human Body of Some Isomers of Tartaric Acid," Journal of the American Pharmaceutical Association, Scientific Edition, *46*:575–578, 1957.

(2) Finkle, P.; "The Fate of Tartaric Acid In The Body," Journal of Biological Chemistry, *100*:349–355, 1933.

(3) Fitzhugh, O. G., and Nelson, A. A.; "The Comparative Toxicities of Fumaric, Tartaric, Oxalic, and Maleic Acids," Journal of the American Pharmaceutical Association, Scientific Edition, *36*:217–219, 1947.

(4) Krop, S., and Gold, H.; "On The Toxicity of Hydroxyacetic Acid After Prolonged Administration Comparison With Its Sodium Salt and Citric and Tartaric Acids," Journal of the American Pharmaceutical Association, Scientific Edition, *34*:86–89, 1945.

(5) Post, W. E.; "The Effect of Tartrates on the Human Kidney," Journal of the American Medical Association, *62*: 592, 1914.

(6) Robertson, B., and Lonnel, L.; "Human Tartrate Nephropathy," Acta Pathologica et Microbiologica Scandinavica, *74*:305, 1968.

(7) Weiss, J. M.; Downs, C. R.; Corson, H. P.; "Inactive Malic Acid As A Food Acidulent," Industrial and Engineering Chemistry, *15*:628–30, 1923.

(8) World Health Organization, Technical Report Series 309; "Specifications for the Identity and Purity of Food Additives and Their Toxicological Evaluation: Food Colours and Some Anti-microbials and Anti-oxidants," World Health Organization, Geneva, Switzerland, 1965.

C. *Labeling.* In addition to the specific labeling [IA and IB], the Panel concludes that the following general principles also apply for truthful and accurate labeling.

1. Various types of burning distress felt in the upper abdomen retrosternally or in the throat may be related to the regurgitation of acid gastric contents into the esophagus, or to other mechanisms in which a reasonable possibility exists that gastric acid is involved. The Panel concludes that antacids are truthfully and accurately promoted to alleviate such symptoms as "heartburn," "sour stomach," and "acid indigestion." These symptoms probably are related to gastric acid, although the evidence is far from conclusive. The mechanism of heartburn is generally believed to be regurgitation of acid gastric contents in the esophagus.

2. The label of every OTC antacid should declare the quantitative composition for all active ingredients.

This composition should be given per tablet, per capsule, or other solid dosage form, per unit volume of liquid used in expressing dose, per packet, or per packet combination.

3. The recommended maximum dosages should be qualified by the phrase: "except under the advice and supervision of a physician."

4. If the maximum daily dose of a given antacid is used daily for more than 2 weeks, a physician should be consulted. Prolonged use of certain agents may be harmful. The label of every antacid should thus contain the following statements or their equivalents: "Do not take more than ____ (maximum recommended daily dosage expressed in units such as tablets or teaspoonfuls) in a 24-hour period except under the advice and supervision of a physician. Do not use the maximum dosage of this antacid for more than 2 weeks except under the advice and supervision of a physician."

5. Depending on dose taken and individual susceptibility, some antacid products may have either a laxative or a constipating effect. Products that cause either of these effects in 5 percent or more of persons using the maximum recommended dose should be so labeled.

Comment. The Panel suggests that the FDA use the clinical impression of experts to identify agents that should be labeled as either laxative or constipating or both, according to the definition given above, until the results of valid clinical studies are available. Studies should be required comparing frequency, water content, and daily weight of stools in control and test periods.

6. OTC antacid products are used to alleviate not only the symptoms of minor upper gastrointestinal complains but also major disorders such as peptic ulcer. The Panel has not reviewed or considered ethical labeling of OTC products as it relates to major disorders such as peptic ulcer, gastritis, and peptic esophagitis. The ethical labeling of antacids should be reviewed by the Food and Drug Administration in light of the conclusions and recommendations of this report.

7. A variance from any labeling requirement defined by this report should be permitted by the Food and Drug Administration only when the application for variance is accompanied by creditable scientific evidence that the requirement does not correctly apply to the product in question.

D. *Drugs combining antacid and other active ingredients.* The Panel concludes that there is no valid scientific evidence that the addition to an OTC antacid of an active ingredient that is neither an antacid nor a corrective for an antacid side effect, will contribute to the product's safety and effectiveness for use antacid therapy alone. The addition nonantacid or noncorrective ingredien may, in fact, reduce the safety or effectiveness of the antacid product.

If antacid combinations are to be al- , the use of the combination of an d and an active ingredient that ther an antacid nor a corrective for an antacid side effect should be limited to those individuals who concurrently have symptoms which require for their relief the pharmacologic action of both the antacid and nonantacid ingredient. This dual indication should be clearly stated on the product label.

1. The Panel concludes that it is rational to combine an antacid with an analgesic if the individual who uses the product has concurrent symptoms which require the relief provided by both types of active ingredients. The indication section of the labeling should state clearly that the combination should be used for heartburn and/or acid indigestion and/or sour stomach only when these symptoms are accompanied by indications for an analgesic. Such a product is not appropriate for peptic ulcer and related disorders. Any analgesic ingredient that is generally recognized as safe and effective (see analgesic Monograph) may be used as the analgesic ingredient.

2. The Panel concludes that it is rational to include a nonantacid laxative ingredient in an antacid if the laxative is solely for the purpose of counteracting the constipating action of one or more of the antacid ingredients. Any laxative action ingredient that is generally recognized as safe and effective (see laxative Monograph) may be used as the laxative ingredient. No labeling claim for the laxative effect would be truthful, because mount of nonantacid laxative in- nt present should not cause laxa- ut only counteract the constipat- effect of the antacid.

Comment. Any other combination of antacid with nonantacid active ingredients should be permitted by the Food and Drug Administration only after it is shown that the conditions for a combination drug set out in the regulations have been met. The Panel is unaware of any other such combinations which meet these conditions at the present time.

II. *Conditions under which antacid products are not generally recognized as safe and effective or are misbranded.* The use of antacids under the following conditions is unsupported by scientific data, and in many instances by sound theoretical reasoning. The Panel concludes that the ingredients, labeling, and combination drugs involved should be removed from the market until scientific testing supports their use.

A. *Active ingredients.* No active ingredients for which data were submitted to the Panel and that is not included in Category I or Category III has, in the Panel's opinion, been shown by adequate and reliable scientific evidence to be safe and effective.

B. *Labeling.* The Panel 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 disturb- s," "excessive smoking," "food in- nce," consumption of "alcoholic ages," "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. Although the Panel is cognizant of the validity of combining an antacid with aspirin for the purpose of buffering the aspirin and for treatment of concurrent symptoms, it concludes that fixed antacid-aspirin combinations are irrational for antacid use alone and therefore should 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.

In experiments in man and animals unbuffered aspirin causes greater visible gastric mucosal damage and more gastrointestinal blood loss than strongly buffered aspirin in solution, which causes little or none of these experimental forms of damage. However, the actual clinical condition of major gastrointestinal hemorrhage associated with aspirin ingestion has been seen with both unbuffered and strongly buffered aspirin in solution. There is inadequate evidence to establish whether the risk of clinically major gastrointestinal hemorrhage is less with strongly buffered aspirin in solution than with unbuffered aspirin. Because of this uncertainty 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.

CITATIONS

(1) Brodie, D. A. and Chase, B. J.; "Role of Gastic Acid in Aspirin-Induced Gastric Irritation in the Rat," Gastroenterology, *53*:604–610, 1967.

(2) Brown, R. K. and Mitchell, N.; "The Influence of Some of the Salicyl Compounds (and alcoholic beverages) on the Natural History of Peptic Ulcer," Gastroenterology, *31*:198–203, 1956.

(3) Grossman, M. I.; Matsumoto, K. K.; Lichter, R. J.; "Fecal Blood Loss Produced by Oral and Intravenous Administration of Various Salicylates," Gastroenterology, *40*:383–388, 1961.

(4) Jennings, G. H.; "Causal Influences in Haematemesis and Melaena," Gut, *6*:1–13, 1965.

(5) Langman, M. J. S.: "Epidemiological Evidence for the Association of Aspirin and Acute GI Bleeding," Gut, *11*:627–634, 1970.

(6) Leonards, J. R. and Levy, G.; "Reduction or Prevention of Aspirin-Induced Occult Gastrointestinal Blood Loss in Man," Clinical Pharmacology and Therapeutics, *10*:571–575, 1969.

(7) Thorsen, W. B. Jr.; Western, D.; Tanaka, Y. and Morrissey, J. F.; "Aspirin Injury to the Gastric Mucosa, Gastrocamera Observations of the Effect of pH," Archives of Internal Medicine, *121*:499–506, 1968.

2. The Panel 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 pharmacoloic 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.

The same conclusions apply to combinations of antacids with sedative-hypnotic ingredients.

3. The Panel 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 nonantacid laxative ingredient.

The Panel recognizes that there are active antacid ingredients that may be effective as laxatives at higher doses than those used for antacid action. The Panel understands that the question whether such uses are appropriate will be reviewed by the Laxative Panel and, for this reason, takes no position on use of these ingredients as laxatives.

4. The Panel 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 to the product's effectiveness.

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

III. CONDITIONS FOR WHICH THE AVAILABLE DATA ARE INSUFFICIENT TO PERMIT FINAL CLASSIFICATION AT THIS TIME

A. *Claimed Active Ingredients.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the active ingredients listed below. These ingredients have either no or negligible antacid action and there is inadequate evidence for their effectiveness for their nonantacid action in the relief of upper gastrointestinal symptoms or in their adjuvant or corrective properties. The Panel believes 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 provided any product that claims to be an antacid (i.e., neutralize stomach acid) meets the general in vitro antacid effectiveness standard. (See monograph.) If adequate effectiveness data are not obtained within 2 years, however, these ingredients listed in this category should no longer be permitted, even in a product that meets the general in vitro antacid effectiveness standard, because of a lack of evidence that these ingredients make a meaningful contribution to the claimed effects.

Active ingredients:
Alginic acid.
Attapulgite, activated (absorbent).
Charcoal.
Gastric mucin.
Kaolin.
Methylcellulose.
Pectin.
Simethicone.
Carboxy methylcellulose.

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 Panel concludes that present evidence is insufficient to demonstrate the effectiveness of this characteristic. 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 Panel 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. *Simethicone.* Although it is reasonably certain that antifoaming agents, by their surface action, cause small gas bubbles to coalesce and form larger ones, whether such a change in size of gas bubbles is clinically beneficial has not been clearly demonstrated. Controlled studies submitted by industry do report a lessening of postoperative gas pains and amounts of gaseous accumulation as judged by X-ray. However, studies with respect to gas accumulation under ordinary conditions of life under which OTC antacids are normally used are limited and not well controlled. Finally, it is far from certain that many of the sensations of "gas" of which patients complain are actually produced by accumulations of gas.

The Panel concludes simethicone to be safe in amounts usually taken orally (e.g., 350 mg) to 500 mg per day) in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time.

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

CITATION

(1) *AMA Drug Evaluations-1971,* 1st Edition, American Medical Association, page 600.

4. *Charcoal, activated.* The Panel 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: "Do not take this product concurrently with a prescription drug except on the advice of your physician or pharmacist." Study is specifically needed to determine whether the charcoal used contains benzpyrene or methylcholanthrane type carcinogens.

Comment. The recommendation that the consumer who purchases an OTC drug should consult with a pharmacist is based on the belief that the pharmacist will be readily available to the purchasing consumer, and that the average U.S.A. pharmacist today is as well acquainted with the subject of possible drug interactions as the average physician. As a specialist in the field he possesses knowledge of the subject or is apt to have appropriate written material (e.g., handbook, manuals, drug interaction lists) readily available. The Panel believes the pharmacist may be able to provide useful understandable information to the consumer which would be inappropriate on an OTC label.

5. *Kaolin.* The Panel 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 comments made under the heading Aluminum [I–B(1)] dealing with the untoward effects of that ingredient on the absorption of other drugs also apply to kaolin.

6. *Methylcellulose.* The Panel 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. *Nitrates.* The Panel concludes nitrates to be safe in amounts usually taken orally (e.g., 0.5 grams maximum per day) in antacid products, and believes it unnecessary to impose a specific dosage limitation at this time. The Panel is aware of the nitrosamine hypothesis but concludes that there is insufficient evidence of lack of safety to justify precluding the use of nitrate in antacids at this time.

8. *Attapulgite (activated).* The Panel 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.

9. *Gastric mucin.* The Panel 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.

10. *Pectin.* The Panel 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.

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 changes in gastric acidity. The Panel concludes that companies marketing products that make claims for alleviation of these or other similar symptoms should 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. But 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 provide by that time should be withdrawn.

Comments. This section pertains to the relief of upper gastrointestinal symptoms claimed for an "antacid" product on the basis of action unrelated to its acid neutralizing capacity. For example, in a patient with total gastric anacidity, an agent might conceivably relieve gastric discomfort by altering gastroduodenal motor function.

2. The Panel concludes that claims or indications which link certain signs and symptoms, such as "sour breath," "upper abdominal pressure," "full feeling," "nausea," "stomach distress," "gas," "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

...w conclusions as to the cause or ...mediation of such symptoms, a con...on that even the medical profession ...ncapable of drawing at this time. Therefore, 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 2 years.

Comment. This section refers to claims that the symptoms listed are related to gastric acidity. Once it is demonstrated that such symptoms and gastric acidly are related, antacids could logically be recommended for such symptoms.

3. The Panel concludes that the evidence currently available is inadequate to support the claim that such Properties as "floating," "coating," "defoaming," "demulcent," "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 should also be completed within 2 years.

INACTIVE INGREDIENTS

A wide variety of pharmaceutical necessities and excipients are used to manufacture antacid products. Examples are fillers, tablet lubricants and binders, disintegrating agents, colorants, flavoring agents, preservatives, suspending agents, and sweeteners. Except for lactose and talc, the Panel did not consider ...status of these inactive ingredients. ...hough the Panel has not considered ...e ingredients, it is the view of the ...anel that their safety and the advisability of listing them on the label be reviewed by an appropriate body. Since these materials are used in the formulation of many drugs other than antacids, it is not appropriate that they be dealt with specifically and solely in relation to antacids.

1. *Lactose.* Although lactose is used in OTC antacid products as an inactive ingredient, concern has been expressed that the lactose content of some products may be sufficient to cause untoward effects in persons who are lactase deficient. Most patients who have lactase deficiency are only partially deficient and can tolerate a glass of milk daily, i.e., 10 grams of lactose. The Panel therefore concludes that the maximum daily consumption of lactose in an antacid product should be limited to 5 grams.

Comment. Five grams of lactose is the amount present in one-half glass of milk. Although numerous studies indicate that about 20 percent of Caucasians and 80 percent of non-Caucasians have some degree of lactose intolerance because of lactase deficiency, only a small percentage of those who are lactase deficient cannot tolerate the amount of lactose here suggested.

CITATION

...tter solicited by Panel chairman ...Bayless, T. M., included in the pub... file.

2. *Talc.* Because of the known carcinogenic effect of asbestos, and because some talcs have been inherently contaminated with asbestos, the Panel is concerned about the inclusion of talc in some antacid preparations. The use and nature of talc in a variety of pharmaceutical preparations warrants study by the Food and Drug Administration.

DATA PERTINENT FOR ANTACID INGREDIENT EVALUATION [1]

CLINICAL TOXICOLOGICAL DATA

A. Minimal lethal dose in man, by single oral ingestion.

B. Maximal tolerated dose in man, by single oral ingestion.

C. Minimal lethal dose in man, taken in divided doses at intervals stated or implied on or construable from product label.

D. Maximal tolerated dose in man, taken in divided doses at intervals stated or implied on or construable from product label.

E. Chronic toxicity in man, especially with respect to renal function and pathology, bone pathology, and any pathologies suggested from experiments in animals.

F. If there are insufficient human data, similar experimental data on omnivorous primates or other suitable species are needed.

ABSORPTION, FATE, DISTRIBUTION, AND EXCRETION

A. The percent of absorption in man of various oral doses, determined by modern methods.

B. The percent of renal excretion in man with various oral doses, determined by modern methods.

C. The metabolic fate in man of absorbed but unexcreted drug.

D. The fate of unabsorbed drug in man, determined by modern methods.

E. The net bioavailability of the drug in man.

F. The ion(s) associated with fecally excreted drug and/or its unabsorbed intraluminal biotransformation products.

G. The ion(s) associated with renally excreted drug and/or its renally excreted biotransformation product.

EFFECTS

A. Effects or oral drug on intragastric, intraintestinal, and gastrointestinal mucosal ion concentration.

B. Effects of oral drug on absorption of ions.

C. Effects of oral drug on renal excretion of ions.

D. Effects of oral drug on blood ion concentration.

E. Effects of oral drug on absorption of phosphate.

F. Effects or oral drug on renal excretion of phosphate.

G. Effects of oral drug on absorption of actively transported substances.

H. Effects of oral drug on absorption of essential nutrients.

I. Effects of oral drug on absorption of other drugs.

J. Effects of oral drug on secretion of gastrointestinal enzymes and bile.

K. Acute and chronic effects of drug on urinary pH and bicarbonate.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 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 of Food and Drugs proposes that Subpart D of Part 130 be amended, pursuant to the recommendations of the Advisory Review Panel on Over-the-Counter Antacid Drugs, by adding a new § 130.305, effective 6 months after publication of the final Monograph in the FEDERAL REGISTER, to read as follows:

§ 130.30[illegible] 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 § 130.3[illegible].

(a) *Active Ingredient(s).* The active ingredient(s) of the product consist(s) of one or more of the ingredients permitted in paragraphs (2) through (14) 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 stipulation need 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.

(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.

[1] Each ingredient requires separate consideration and may justify additional testing.

(c) Place empty beaker on stirrer, add stirring bar, determine setting for stirring at 240 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 240 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 paragraph (g) of this section is 3.5 or greater, add 1.0 N HCl from buret to bring pH to 3.5. Continue to add 1.0 N HCl at the rate required to hold pH at 3.5.

(i) Exactly 5 minutes after beginning addition of 1.0 N HCl (15 minutes after adding antacid) read and record ml. of 1.0 N HCl used.

(j) Calculation: 5 mEq. (in 50 ml. 0.1 N HCl used in 1st 10 min.) + number of ml. 1.0 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 carlbonate.

(ii) Aluminum hydroxide (as aluminum hydroxide-hexitol stabilized 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 12.5 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.*

(i) Sodium bicarbonate or carbonate, maximum daily dosage limit 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 except under the advice and supervision of a physician."

(2) "Do not use the maximum dosage of this antacid for more than 2 weeks except under the advice and supervision of a physician."

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

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

(5) 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."

(6) 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."

(7) 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 ha kidney disease."

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

(e) *Statement of active ingredients.*

(1) The labeling of the product contains the quantitative amount of each active ingredient, expressed in terms of the dosage unit stated in the directions for use (e.g., tablet, teaspoonful).

(2) 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*), 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.

(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 as additional indications peptic ulcer, gastritis, and peptic esophagitis.

(g) *Combination with nonantacid active ingredients.*

(1) An antacid may contain any generally recognized safe and effective nonantacid laxative ingredient (see laxative Monograph) to correct for constipation caused by the antacid. No labeling mention of the laxative ingredient or claim of laxative effect may be used for such a product.

(2) An antacid may contain any generally recognized 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).

(h) *Inactive ingredients.* The amount of lactose in a maximum daily dosage may not exceed 5 gm. per day.

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before June 4, 1973. Such comments should be addressed to the hearing clerk, Department of Health, Education, and Welfare, room 6–88, 5600 Fishers Lane, Rockville, Md. 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before July 2, 1973. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: March 9, 1973.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

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