standard would benefit neither the household nor the industrial consumer, or the sugar manufacturer. It pointed out that the terms "soft white" and "soft sugar" are not the common or usual names for any of the sugar products distributed in the United States within the specifications provided by the standard.

Having considered all the comments received, FDA has concluded that there is neither sufficient interest nor need to warrant proposing U.S. standards at this time for soft sugars under the authority of section 401 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 341).

Therefore, under the procedures in 21 CFR 130.6, notice is given that the Commissioner of Food and Drugs has terminated consideration of developing U.S. standards for soft sugars based on the Codex standard. This action is without prejudice to further consideration of the development of U.S. standards for soft sugars upon appropriate justification.

The Codex Alimentarius Commission will be informed that an imported food that complies with the requirements of the Codex standard for soft sugars may move freely in interstate commerce in this country, providing it complies with applicable U.S. laws and regulations.

Dated: October 11, 1979.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 79-32116 Filed 10-18-79; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Part 310

[Docket No. 79N-0176]

Stomach Acidifier Drug Products for Over-the-Counter Human Use; Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This document proposes that stomach acidifier drug products be classified in Category II as being not generally recognized as safe and effective or as being misbranded for over-the-counter (OTC) use. The document, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by January 17, 1980, and reply comments by February 18, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on June 23, 1978, a report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner of Food and Drugs issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded (i.e., Category I); (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding (i.e., Category II); (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify such conditions under either (1) or (2) above (i.e., Category III); and (4) the conclusions and recommendations of the Panel. Because the Panel's recommendations on stomach acidifier drug products for OTC use contain no Category I or Category III conditions, FDA is therefore issuing the Panel's recommendations as a notice proposing Category II classification of stomach acidifier drug products for OTC use.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. The Panel's findings appear in this document as a formal notice to propose classification of stomach acidifer drug products as Category II and to obtain public comment before the agency reaches any decision on the Panel's recommendations. Should the agency accept the Panel's recommendation that the ingredients in stomach acidifier drug products be classified as Category II, a regulation declaring the products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) will be proposed for inclusion in Part 310, Subpart E (21 CFR Part 310, Subpart E). The agency is including the proposed regulation in this notice to obtain full public comment at this time. After FDA has carefully reviewed the comments and reply comments, submitted in response to this notice, the agency will issue a tentative final order on stomach acidifier drug products for OTC use.

Should FDA accept the conclusions and recommendations of the Panel, the agency would propose that stomach acidifier drug products be eliminated from the OTC market, effective 6 months after the date of publication of a final order in the **Federal Register**, regardless of whether further testing is undertaken to justify their future use.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning stomach acidifier drug products for OTC use submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information will be put on public display in the office of the Hearing Clerk, Food and Drug Administration, after November 19, 1979, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address given above).

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). In the **Federal Register** of August 27, 1975 (40 FR 38179), a further notice supplemented the initial notice with a detailed list of ingredients which included stomach acidifier ingredients.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of the ingredients in those products: John

W. Norcross, M.D., Chairman, Ruth Eleanor Brown, R.Ph. (resigned May 1976), Elizabeth C. Giblin, Ed.D., Richard D. Harshfield, M.D., Theodore L. Hyde, M.D., Claus A. Rohweder, D.O., Samuel O. Thier, M.D. (resigned November 1975), William R. Arrowsmith, M.D. (appointed March 1976), Diana F. Rodriguez-Calvert, Pharm.D. (appointed July 1976).

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D., Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm.D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph.D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator. Enrique Fefer, Ph.D., served as the Executive Secretary until July 1976, followed by George W. James, Ph.D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph.

To expand its medical and scientific base, the Panel called upon the following consultant for advice in areas which required particular expertise: Ralph B. D'Agostino, Ph.D. (statistics).

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs, but due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for stomach acidifier drug products in this document. The review of all other categories of miscellaneous internal drug products will be continued by the Panel, and its findings will be periodically published in the **Federal Register** during the Panel's deliberations.

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings were held on the following dates (the dates of those meetings which dealt with the topic of this document are in italics): February 23 and 24, *March 23 and 24, April 27 and 28,* June 22 and 23, September 21 and 22, November 16 and 17, 1975; February 8 and 9, *March 7 and 8,* April 11 and 12, *May 9 and 10,* July 11 and 12, *October 10 and 11,* 1976; *February 20 and 21,* April 3 and 4, May 15 and 16, July 9, 10, and 11, October 15, 16, and 17, December 2, 3, and 4, 1977; *January 28, 29, and 30, March 10, 11, and 12, May 5, 6, and 7,* and *June 23, 24, and 25,* August 4, 5, and 6, September 29, 30, and October 1, November 17, 18, and 19, 1978; January 19 and 20, and *March 2 and 3,* 1979.

The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA–305), Food and Drug Administration (address given above).

The following individuals were given an opportunity to appear before the Panel to express their views on stomach acidifier drug products for OTC use, either at their own or at the Panel's request: C. N. Christensen, M.D., John M. Holt, C. H. Sun, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through June 23, 1978 in arriving at its conclusions and recommendations for OTC stomach acidifier drug products.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered stomach acidifier drug products for OTC use with respect to the following three categories:

Category I. Conditions under which stomach acidifier drug products are generally recognized as safe and effective and are not misbranded for OTC use.

Category II. Conditions under which stomach acidifier drug products are not generally recognized as safe and effective or are misbranded for OTC use.

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

The Panel concludes that all stomach acidifier active ingredients reviewed are safe, but none is effective for OTC use (Category II) in relieving the conditions of achlorhydria and hypochlorhydria.

A. Ingredients Reviewed by the Panel

Pursuant to the notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on OTC miscellaneous internal drug products, the following firms made submissions related to products used as stomach acidifiers:

1. *Submissions by Firms*

Firms	*Marketed products*
Eli Lilly & Co., Indianapolis, IN 46206	Acidulin.
Stuart Pharmaceuticals, Wilmington, DE 19899	Normacid.
Winthrop Laboratories, New York, NY 10016.	Acidol-Pepsin.

2. *Labeled ingredients contained in marketed products*—a. *Ingredients in drug products submitted to the Panel for review.*

Betaine hydrochloride
Glutamic acid hydrochloride
Pepsin

b. *Other ingredients reviewed by the Panel.* In addition to those ingredients contained in submitted products, the following ingredient, which was included in the **Federal Register** notice of August 27, 1975 (40 FR 38179) and for which no data were received, was reviewed by this Panel:

Diluted hydrochloric acid.

3. *Classification of ingredients*—a. *Active ingredients.*

Betaine hydrochloride
Glutamic acid hydrochloride
Diluted hydrochloric acid
Betaine hydrochloride and pepsin

b. *Inactive ingredients.*

None.

B. Referenced OTC Volume Submissions

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the submitted information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on display after November 19, 1979, in the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857.

C. Definition of Terms

For the purposes of this document, the Panel agreed on the following definitions:

1. *Stomach acidifier.* An agent which adds hydrochloric acid to the stomach.

2. *Achlorhydria.* An absence of secretion of hydrochloric acid by the stomach even after suitable stimulation.

3. *Hypochlorhydria.* A subnormal secretion of hydrochloric acid by the stomach even after suitable stimulation.

4. *Diluted hydrochloric acid.* As described in the 19th Edition of the "United States Pharmacopeia."

D. General Discussion

The Panel was charged with the review of numerous pharmacologic categories of OTC drug products, including those which are known as stomach acidifiers. The Panel has reviewed the available data and has evaluated the safety and effectiveness of stomach acidifiers for OTC use.

The Panel agrees that in some individuals the stomach secretes a subnormal amount of hydrochloric acid (hypochlorhydria) and that in some other individuals the stomach secretes no hydrochloric acid (achlorhydria). In the past, drug products containing ingredients such as betaine hydrochloride, glutamic acid hydrochloride, and diluted hydrochloric acid have been employed as a means of normalizing the hydorchloric acid content of the stomach. Although the Panel recognizes that each of these ingredients in recommeded doses adds hydrochloric acid to the stomach, the Panel believes that such treatment is not clinically beneficial.

More important, the Panel believes that because the conditions of achlorhydria and hypochlorhydria do not produce any symptoms (i.e., they are asymptomatic), these conditions are not amenable to self-diagnosis. Therefore, the Panel concludes that all ingredients used to treat the conditions of achlorhydria and hypochlorhydria are Category II for OTC use.

E. Physiology Review

To evaluate the ingredients under review, the Panel considered the role of hydrochloric acid in digestion and the regulatory mechanisms that control its secretion. The acidity of the stomach depends in part upon the rate of secretion of hydrochloric acid. The basal rate is almost 30 milliliters (mL) of a dilute solution of hydrochloric acid per hour. The basal secretion rate ranges from 0 to 17 milliequivalents (meq) per hour (Refs. *1* and *2*). Following a meal, there is about a 25 percent increase in the secretion of hydrochloric acid.

The secretion of hydrochloric acid is stimulated by a number of factors, including sight, smell, and taste of food; distention of the stomach; and the release of the hormone gastrin. Gastrin is released by the presence of protein digestive products, caffeine, or alcohol. The secretion of acid is inhibited by a reflex from the duodenum which inhibits both the release of gastrin and the secretion of the gastric glands. Distention of the duodenum and the presence of acid, fats, or a hypertonic solution activate the reflex inhibition of the secretions.

Hydrochloric acid assists digestion by converting pepsinogen to pepsin. Together with pepsin, hydrochloric acid breaks up connective tissue and cell membranes and reduces the size of food particles on the surface of the food mass in the stomach. However, hydrochloric acid is not essential for the digestion and absorption of food.

References

(*1*) Davenport, H., "Physiology of the Digestive Tract," 3d Ed., Year Book Publishers, Inc., Chicago, pp. 143–153, 1971.

(*2*) Vander, S., J. Sherman, and D. Luciano, "Human Physiology, Mechanisms of Body Function," McGraw-Hill, New York, pp. 378–384, 1970.

F. Category II Active Ingredients

The Panel has classified the following stomach acidifier ingredients as not generally recognized as safe and effective or as being misbranded for OTC use in treating self-diagnosed conditions of achlorhydria and hypochlorhydria:

Betaine hydrochloride
Glutamic acid hydrochloride
Diluted hydrochloric acid
Betaine hydrochloride and pepsin

1. *Betaine hydrochloride.* The Panel concludes that betaine hydrochloride is safe in the dose stated below but not generally recognized as effective in treating achlorhydria and hypochlorhydria.

a. *Safety.* The oral dosage range of betaine hydrochloride used as a substitute for hydrochloric acid is 0.5 to 3.0 grams (g) (Ref. *1*) with a dose of 0.5 g equivalent to approximately 1.1 mL of diluted hydrochloric acid (Ref. *2*). The Panel has been unable to find any reports of adverse reactions to betaine hydrochloride in the medical literature.

There is no information, to the Panel's knowledge, to indicate that betaine hydrochloride is unsafe in the usual oral dose of 0.44 g administered three times daily with meals (Ref. *3*).

b. *Effectiveness.* Due to its ease of administration and its lack of erosive effect on tooth enamel, betaine hydrochloride is sometimes given as a substitute for diluted hydrochloric acid. The usual recommended dose of betaine hydrochloride delivers less hydrochloric acid to the stomach than does the usual recommended dose of diluted hydrochloric acid. There are no controlled studies showing that even large amounts of hydrochloric acid are efficacious in aiding digestion (Ref. *4*). Currently marketed products contain an amount of betaine hydrochloride that is equivalent to between 0.67 and 1.0 mL of diluted hydrochloric acid in a single dose.

Betaine hydrochloride is claimed to be beneficial to persons with low or nonexistent gastric acid secretion because it is said to help in providing a more optimal pH for enzymatic activity in the stomach (Refs. *5* and *6*). However, the Panel has not been presented with, nor is it aware of, convincing evidence demonstrating the effectiveness of hydrochloric acid in the treatment of achlorhydria and hypochlorhydria.

c. *Evaluation.* The Panel concludes that betaine hydrochloride is generally recognized as safe in the dose specified, but its effectiveness has not been demonstrated for the treatment of achlorhydria and hypochlorhydria. In fact, the Panel is of the opinion that such conditions are asymptomatic and, therefore, not amenable to self-diagnosis.

References

(*1*) Stecher, P. G., "The Merck Index," 8th Ed., Merck and Co., Inc., Rahway, NJ, p. 145, 1968.

(*2*) Swinyard, E. A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A., and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 738, 1975.

(*3*) OTC Volume 170011.

(*4*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 1082–1083, 1977.

(*5*) OTC Volume 170023.

(*6*) OTC Volume 170049.

2. *Glutamic acid hydrochloride.* The Panel concludes that glutamic acid hydrochloride is safe in the dose stated below but not generally recognized as effective in treating achlorhydria and hypochlorhydria.

a. *Safety.* The oral dosage range of glutamic acid hydrochloride is 0.6 to 1.8 g three times daily (Refs. *1* and *2*). A dose of 0.3 g corresponds to 0.6 mL of diluted hydrochloric acid (Ref. *1*). The Panel has determined that glutamic acid hydrochloride is safe in the usual oral dose of 1.02 g administered three times daily (Ref. *3*). No adverse reactions have been reported in the literature at this dose.

b. *Effectiveness.* Glutamic acid hydrochloride is claimed to increase the amount of hydrochloric acid present in the stomach, thus altering the pH of the gastric environment (Refs. *4* and *5*). Due to its ease of administration and its lack of erosive effect on tooth enamel, glutamic acid hydrochloride is sometimes used as a substitute drug for diluted hydrochloric acid. The usual recommended dose of glutamic acid hydrochloride delivers less hydrochloric acid to the stomach than does the usual recommended dose of diluted hydrochloric acid. There are no controlled studies showing that even

large amounts of hydrochloric acid are efficacious in aiding digestion (Ref. *6*). The Panel has not been presented with, nor is it aware of, any convincing evidence demonstrating the effectiveness of hydrochloric acid in the treatment of achlorhydria and hypochlorhydria.

c. *Evaluation.* The Panel concludes that glutamic acid hydrochloride is generally recognized as safe in the dose specified, but its effectiveness has not been demonstrated for the treatment of achlorhydria and hypochlorhydria. In fact, the Panel is of the opinion that such conditions are asymptomatic and, therefore, not amenable to self-diagnosis.

References

(*1*) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott, Philadelphia, pp. 559–560, 1973.

(*2*) Swinyard, E. A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A., and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 737, 1975.

(*3*) OTC Volume 170103.

(*4*) OTC Volume 170023.

(*5*) OTC Volume 170049.

(*6*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 1082–1083, 1977.

3. *Diluted hydrochloric acid.* The Panel concludes that diluted hydrochloric acid is safe when taken in the dose stated below but not generally recognized as effective for treating achlorhydria and hypochlorhydria.

a. *Safety.* Diluted hydrochloric acid contains 10 percent hydrochloric acid and is usually given in a dose of 5 mL, further diluted with 125 to 250 mL of water (Ref. *1*). This amount of hydrochloric acid is considered safe for oral administration when the solution is sipped through a glass straw to minimize tooth enamel erosion by the acid.

b. *Effectiveness.* While diluted hydrochloric acid does somewhat increase the acidity of the gastric contents, the usual therapeutic dose is generally not sufficient to result in free hydrochloric acid in the stomach in the case of achlorhydria (Refs. *1* and *2*). Instead, most of the acid is bound by the gastric contents (Ref. *1*). There are also no controlled studies showing that even large amounts of hydrochloric acid are efficacious in aiding digestion (Ref. *2*). The Panel was not presented with, nor is it aware of, any convincing evidence demonstrating the effectiveness of diluted hydrochloric acid in treating achlorhydria and hypochlorhydria.

c. *Evaluation.* The Panel concludes that diluted hydrochloric acid is generally recognized as safe in the dose specified, but its effectiveness has not been demonstrated for the treatment of achlorhydria and hypochlorhydria. In fact, the Panel is of the opinion that such conditions are asymptomatic and, therefore, not amenable to self-diagnosis.

References

(*1*) Harvey, S. C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S., and A. Gilman, The MacMillan Co., New York, pp. 970–971, 1975.

(*2*) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 1082–1083, 1977.

4. *Betaine hydrochloride and pepsin.* Two submissions were received for a product containing betaine hydrochloride and pepsin. This combination was labeled as a stomach acidifier. No data were submitted, nor is the Panel aware of any, which substantiate a claim that pepsin functions as a stomach acidifier or enhances the stomach-acidifying effects of betaine hydrochloride. The Panel concludes that this is a safe combination but not effective in treating the conditions of achlorhydria and hypochlorhydria. Therefore, the Panel recommends that betaine hydrochloride and pepsin be included in Category II. (In a future issue of the **Federal Register**, the Panel will review pepsin as a digestive aid ingredient.)

G. Category II Labeling

The Panel reviewed the labeling claims made for the submitted drug products and concludes that each of the stomach acidifier ingredients reviewed is safe but not effective for the treatment of achlorhydria and hypochlorhydria in the dose specified. In addition, and more important, the Panel believes that these conditions do not produce any symptoms and therefore should not be considered as symptomatic disease states. For these reasons, the Panel has classified the following labeling claims as Category II and not appropriate for OTC use:

1. For hydrochloric acid deficiency.
2. For replacement therapy in deficiencies of hydrochloric acid in gastric secretion.
3. Stomach acid medication.
4. For achlorhydria.
5. For stomach subacidity.
6. Assists digestion in gastric hypoacidity by gradual release of hydrochloric acid and pepsin.
7. Digestant.

The Food and Drug Administration has determined that this document is exempt from the requirement of preparing an Environmental Impact Statement as specified under 21 CFR 25.1(f)(4).

Therefore, under 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, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 310 by adding new § 310.540, to read as follows:

§ 310.540 OTC drug products containing active ingredients offered for use as stomach acidifiers.

(a) Betaine hydrochloride, glutamic acid hydrochloride, diluted hydrochloric acid, and pepsin have been present as ingredients in over-the-counter (OTC) drug products for use as stomach acidifiers. Based upon the lack of adequate data to establish the effectiveness of these or any other ingredients of stomach acidifiers used in treating achlorhydria and hypochlorhydria, and because such conditions are asymptomatic and not amenable to self-diagnosis, any OTC drug product containing ingredients offered for use as stomach acidifiers cannot be considered generally recognized as safe and effective.

(b) Any OTC drug product labeled, represented, or promoted as a stomach acidifer is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, presented, or promoted as a stomach acidifier for OTC use is safe and effective for the purpose intended.

(d) Any such drug product introduced in interstate commerce after the effective date of a final regulation that is not in compliance with this section is subject to regulatory action.

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before January 17, 1980. Comments should be addressed to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville,

MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before February 18, 1980. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: October 10, 1979.

Sherwin Gardner,

Acting Commissioner of Food and Drugs.

[FR Doc. 79-32107 Filed 10-18-79; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Part 320

[Docket No. 79N-0133]

Certain Sulfonamide Anti-Infectives; Proposed Bioequivalence Requirements

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) proposes to establish bioequivalence requirements for certain oral sulfonamide drug products used in the treatment of bacterial infections. Available data suggest that the various marketed brands of the same oral sulfonamides may not have comparable therapeutic effects. The proposed regulations would assure the bioequivalence of different brands of such products and batch-to-batch uniformity of the same product by each manufacturer.

DATES: Comments by December 18, 1979; FDA proposes that the final regulation based on this proposal become effective 30 days after the date of its publication in the **Federal Register.**

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

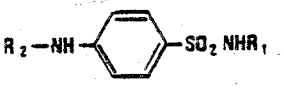
FOR FURTHER INFORMATION CONTACT: Henry J. Malinowski, Bureau of Drugs (HFD-525), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4750.

SUPPLEMENTARY INFORMATION: FDA has promulgated regulations in Subpart C of Part 320 (21 CFR Part 320) setting forth procedures by which the agency may, on its own initiative or in response to a petition from an interested person, propose and promulgate regulations to establish bioequivalence requirements for drug products containing identical amounts of the same active drug ingredient and in the same dosage form that are intended to be used interchangeably for the same therapeutic effect and for which there is a known or potential bioequivalence problem. The Commissioner of Food and Drugs has delegated authority to issue, amend, or repeal these regulations to the Director and Deputy Director of FDA's Bureau of Drugs (21 CFR 5.79).

Data available to FDA demonstrate that there is well-documented evidence of actual bioequivalence differences in oral formulations of sulfadiazine, trisulfapyrimidines, and sulfaphenazole and potential bioequivalence differences in oral formulations of other drugs in the class of sufonamides among currently marketed brands of the same drug product produced by various manufacturers, based on the criteria set forth in § 320.52 (21 CFR 52). Therefore, the Director of the Bureau of Drugs, on the Director's own initiative, tentatively concludes that a bioequivalence requirement involving both in vivo testing in humans and in vitro dissolution testing should be established for acetyl sulfisoxazole emulsion and for the following oral solid dosage form sulfonamides: Sulfachlorpyridazine, sulfacytine, sulfadiazine,sulfadiazine sodium bicarbonate, sulfadimethoxine, sufaethidole, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethoxazole, sulfamethoxypyridazine,sulfaphenazole, sulfapyridine, sulfasalazine, sulfisomidine, trisulfapyrimidines, and sulfadiazine-sulfamerazine-sulfamethazine-sulfacetamide-sulfamethizole combination. The Director also tentatively concludes that, because existing data demonstrate an in vivo/in vitro correlation, (Refs. 22 and 23), a bioequivalence requirement involving only an in vitro bioequivalence standard should be established for sulfisoxazole tablets and for all sulfonamide suspensions. The evidence on which the Director bases these tentative conclusions and the proposed bioequivalence requirements are discussed below (see also Ref. 1).

Background

Orally administered sulfonamides have a wide range of antimicrobial activity. Essentially, they inhibit the growth or multiplication of bacteria; i.e., they are bacteriostatic agents. Although the importance of the sulfonamides in the treatment of infectious diseases has diminished with the development of more effective antimicrobial agents, these drugs continue to have a prominent place in the treatment of lower urinary tract infections and systemic infections caused by *Nocardia* species. They are also drugs of choice for prophylaxis in rheumatic fever and meningococcal infections that are sensitive to sulfonamides. Although no one oral sulfonamide drug product is equally effective in all types of infections, for purposes of bioequivalence requirements the sulfonamides are considered together because they are members of a class of drugs having close structural commonality and similar physicochemical and pharmacological properties. All of them are derivatives of sulfanilic acid and contain the following general structural formula:



Substituents and R_1 and R_2 for some important sulfonamides are shown in Table 1.

BILLING CODE 4110-03-M