DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 82N-0166]

RIN 0905-AA06

Orally Administered Drug Products for Relief of Symptoms Associated With Overindulgence in Food and Drink for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) orally administered drug products for relief of symptoms associated with overindulgence in food and drink (drug products for the relief of symptoms of upset stomach due to overindulgence resulting from food and drink, and drug products to minimize or relieve hangover symptoms) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by April 22, 1992. New data by December 24, 1992. Comments on the new data by February 24, 1993. Written comments on the agency's economic impact determination by April 22, 1992.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 1, 1982 (47 FR 43540), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug products. Interested persons were invited to submit comments by December 30, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 31, 1983.

In accordance with § 330,10(a)(10), the data and information considered by the Panel were placed on public display in the Dockets Management Branch (address above), after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking, two manufacturers, one consumer group, and one individual submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In this tentative final monograph (proposed rule) to establish subpart J of part 357 (21 CFR part 357—subpart J), FDA states for the first time its position on the establishment of a monograph for OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink. The agency has changed the title of this monograph from drug products for * * * overindulgence in "alcohol and food" to * * * "food and drink." The agency considers the terms "food and drink" to be more inclusive of the use of these drug products. Final agency action on this matter will occur with the publication at a future date if a final monography, which will be a final rule establishing a monograph for these drug products.

This proposal constitutes FDA's tentative conclusions on OTC orally administered drug products for relief of symptoms associated with overindulgence in food and drink based on the agency's independent evaluation of the Panel's report and the comments received. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

In the advance notice of proposed rulemaking for these products (47 FR 43540), the Panel's discussion and the recommended monograph were organized into four categories of active ingredients: (1) To minimize inebriation, (2) to minimize hangover symptoms, (3) for relief of hangover symptoms, and (4) for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food. In the **Federal Register** of July 19, 1983 (48 FR 32872), the agency published a notice announcing that fructose or any other ingredient intended to minimize or prevent inebriation is a new drug and is required to be the subject of an approved new drug application (NDA) before marketing.

Activated charcoal, the only ingredient reviewed to reduce or minimize hangover, was placed in Category III in the advance notice of proposed rulemaking (47 FR 43540 at 43555). No additional data have been submitted to the agency to prove the effectiveness of activated charcoal in reducing or minimizing hangover. Therefore, activated charcoal remains in Category III for this use and is not further discussed in this document. However, the agency is proposing Category I labeling in this document in the event that data are submitted which result in the upgrading of activated charcoal to monograph status in the final rule.

In reviewing the Panel's recommendations on OTC drug products for relief of hangover symptoms and OTC drug products for relief of symptoms of upset stomach due to overindulgence in the combination of alcohol and food, the agency recognizes that this rulemaking significantly overlaps other rulemakings in the OTC drug review. For example, the Panel's recommendation on OTC drug products for relief of hangover symptoms consists of a combination of ingredients involving ingredients already classified as Category I in other OTC drug monographs: Antacid (21 CFR part 331), stimulant (21 CFR part 340), and internal analgesic (proposed 21 CFR part 343) (see the **Federal Register** of November 16, 1988, 53 FR 46204). To avoid unnecessary monograph duplication, the agency will not propose to establish a separate monograph for products for relief of hangover symptoms that contain these classes of ingredients. Instead, the agency is proposing to amend the final monographs for OTC antacid (21 CFR part 331) and stimulant (21 CFR part 340) drug products, and is amending the tentative final monograph for OTC internal analgesic drug

products to include appropriate conditions for relief of hangover symptoms. These proposals are published elsewhere in this issue of the Federal Register.

Similarily, the claim for relief of symptoms of upset stomach due to overindulgence in the combination of food and drink overlaps claims contained in the antacid rulemaking. Therefore, the agency is proposing to amend the final monograph for OTC antacid drug products to include appropriate conditions for relief of the symptoms of upset stomach due to overindulgence in food and drink.

Therefore, this tentative final monograph will include only ingredients, such as bismuth subsalicylate, that are not included in other OTC drug final monographs or ongoing rulemakings and only for claims related to relief of upset stomach associated with overindulgence in food and drink. For further discussion, see comment 1 below.

For the sake of clarity and comprehensiveness, all issues raised in comments to the advance notice of proposed rulemaking for OTC orally administered drug products for relief of symptoms associated with overindulgence in alcohol and food (47 FR 43540) are being addressed in this tentative final monograph. However, any comments received in response to the proposed amendments to the monographs for OTC antacid, internal analgesic, or stimulant drug products, published elsewhere in this issue of the Federal Register, will be addressed in the respective rulemaking, as appropriate.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

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 31697) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments

1. Two comments questioned the appropriateness of the term "food and drink overindulgence reliever" as a statement of identity. The comments noted that OTC drug monographs normally use a term such as "antacid" or "analgesic" that describes the pharmacological category or principal intended action of the active ingredient(s) as a statement of identity. One comment requested that terms such as "antacid" or "analgesic" be permitted as alternatives to the Panel's recommended statement of identity. The comment added that consumers are familiar with current statements of identity and proposing new ones may confuse consumers or mislead them into thinking that a product has been changed. The other comment requested that the statement of identity be changed from "food and drink overindulgence reliever" to "upset stomach remedy," stating that this phrase is concise, accurate, and provides the consumer with a better understanding of the product's intended use. The comment added that the Panel's proposed statement of identity is very lengthy and could create labeling space problems, particularly for a product with multiple indications.

The agency acknowledges that statements of identity are normally expressed in terms of the general pharmacological category(ies) or principal intended action(s) of the active ingredients in the products, in accord with 21 CFR 201.61. As pointed out by the comments, the statement of identity "food and drink overindulgence reliever," which was recommended by the Panel, does not conform to the usual practice set forth in § 201.61 and is potentially confusing to consumers. The agency believes that a shorter, more concise statement of identity can be used, and the agency is proposing to revise the statement of identity. The agency believes that the statement of identity "upset stomach remedy" suggested by one of the comments is preferable. However, the agency believes this phrase would be more appropriate if the term "remedy" was replaced with the term "reliever" because the term "reliever" more accurately describes the intended effect of such products than the term "remedy." Therefore, the agency is proposing the term "upset stomach reliever" as the statement of identity for the products covered by this tentative final monograph.

The suggestion by one comment that widely recognized statements of identity such as "antacid" or "analgesic" be allowed as alternatives to the proposed statement of identity is not being included in this document. As discussed in the preamble to this document, if the action of an ingredient or combination of ingredients in relieving "upset stomach" or "overindulgence in food and drink" is that of an antacid, then those ingredients are more appropriately covered under the monograph for OTC antacid drug products and would bear the statement of identity appropriate to that monograph, i.e., "antacid", as the comment requested. (See notice of proposed rulemaking for Antacid Drug

Products for Over-the-Counter Human Use published elsewhere in this issue of the **Federal Register**.)

As discussed above, the agency is limiting this rulemaking to those ingredients, such as bismuth subsalicylate, that are not covered by the rulemaking for OTC antacid drug products. (See section II. paragraph A. 1.)

2. One comment urged that combination drug products containing sodium citrate and sodium acetylsalicylate in solution be exempted from the Panel's recommended analgesic overdose warning regarding ringing in the ears in § 357.952(c)(4)(ii) (47 FR 43540 at 43559). The comment argued that this combination is incapable of producing potentially toxic blood levels of salicylate. The comment stated that, in comparison with aspirin administered in other dosage forms, this combination product produces more rapid, high salicylate blood levels, an increased salicylate excretion rate with increasing dosages due to alkalinization of the urine by the sodium citrate, and a leveling off of plasma salicylate concentration. In support of this argument, the comment referred to a study of Leonards (Ref. 1) in which large repeated doses of the combination drug product or aspirin were administered to human subjects and plasma salicylate levels were determined. Four 325-milligram (mg) tablets of aspirin were given every 2 hours up to a maximum of 20 tablets in 8 hours. Four tablets of the combination drug product, containing an amount of salicylate equivalent to the aspirin, were also given every 2 hours, up to a maximum of 28 tablets in 12 hours. The plasma salicylate levels reached 2 hours after the last dose were 188 milligrams per liter (mg/L) for the combination product and 300 mg/L for aspirin. Plasma salicylate reached approximately 200 mg/L for the combination product at 10 hours, but had dropped to 180 mg/L at 14 hours. Therefore, the comment contended that this combination drug product will not reach toxic plasma salicylate levels, regardless of the dose taken, and the proposed warning should not be applicable to this particular combination drug product.

The agency has reviewed the cited study (Ref. 1) and concludes that the data are inadequate to establish that toxic blood levels of salicylate cannot be achieved by a combination product containing sodium citrate and sodium acetylsalicylate. The study includes two separate dosage tests conducted on two groups of subjects. In the first test, 12 normal adult subjects were given 1,300 mg (4 tablets of 325 mg each) of aspirin followed by 6 ounces (oz) of water every 2 hours until 6.5 grams (g) (20 tablets) were taken. One week later, an equivalent dose of the combination product dissolved in 6 oz of water was administered to the same 12 subjects. Blood samples were taken at 0, 2, 4, 6, 8, and 10 hours after the first dose and total salicylate in plasma was determined. Plasma salicylate levels of approximately 300 mg/L for the aspirin and 188 mg/L for the combination product were reported 2 hours after the last dose. The test indicated that plasma salicylate levels after repeated administration of large amounts of aspirin continued to rise to approach toxic levels, while the plasma salicylate levels after repeated administration of large amounts of the combination drug product appeared to level off at the still safe concentration of 188 mg/L. The second dose test assessed the peak plasma salicylate levels of six subjects given the same amount of combination drug product as used in the first test; the subjects were given the drug every 2 hours until seven doses had been taken. Peak plasma salicylate levels of approximately 200 mg/L were reached 10 hours after the first dose, with the level dropping to approximately 180 mg/L at 14 hours.

The agency acknowledges that the Leonards study shows that subjects who received the combination drug product had lower plasma salicylate levels after 10 hours than those who received aspirin. However, as the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel) discussed in its report (42 FR 35346 at 35379), there is great variability of salicylate metabolism and elimination in normal individuals. Thus, the plasma salicylate levels observed in the small sample of subjects used in the Leonards study (Ref. 1) could not be considered to be representative of the population on a whole. Further, the Internal Analgesic Panel pointed out that no correlation between response and plasma levels has been established (42 FR 35346 at 35373). The Internal Analgesic Panel further noted that correlation between product formulation, drug blood levels achieved, and the onset of pharmacological effect is not understood (42 FR 35346 at 35374). Thus, even if a correlation between dose and plasma salicylate levels can be established, a correlation between plasma salicylate levels and salicylate effect (i.e., ringing in the ears) must still be established. The agency concurs with the Panel's findings. (See also comment 39 of the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products published in the **Federal Register** of November 16, 1988, 53 FR 46204 at 46222.)

Therefore, based on the above discussion, the agency is not exempting combination drug products containing sodium citrate and sodium acetylsalicylate from the warning regarding ringing in the ears. Combinations of antacids and internal analgesics, including combinations of sodium citrate and sodium acetylsalicylate in solution, are primarily being handled in the rulemaking for OTC internal analgesic drug products and not in this rulemaking. (See also comment 1.) Such a combination drug product would, therefore, be required to bear the warning proposed in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products in § 343.50(c)(1)(v)(A), published in the **Federal Register** of November 16, 1988 (53 FR 46204 at 46256), which states "If ringing in the ears or a loss of hearing occurs, consult a doctor before taking any more of this product." Such products would not be permitted to bear the warning recommended by the Miscellaneous Internal Panel in § 357.952(c)(4)(ii) of the advance notice of proposed rulemaking for OTC orally administered drug products for the relief of symptoms associated with overindulgence in alcohol and food.

Reference

(1) Leonards, J. R., "Safety of Alka-Seltzer in Very Large Doses as Evidenced by Plasma Salicylate Levels," draft of unpublished study, OTC Volume 170198, Docket No. 82N-0166, Dockets Management Branch.

3. One comment urged that the claims "fast relief" and "speedy relief" be permitted in the labeling of a drug product containing a combination of sodium citrate and sodium acetylsalicylate in solution. The comment claimed that substantial scientific data submitted to the Panel on this product clearly demonstrate that the product provides faster symptomatic relief than other dosage forms. The comment pointed out that, because this product is already in solution when ingested, the dissolution step that is necessary for other dosage forms before absorption occurs is eliminated. Thus, the acetylsalicylate and total salicylate quickly become available. The comment added that the rapid gastric emptying (to the duodenum) that occurs produces both early and high peak plasma levels of acetylsalicylate (Ref. 1). The commen also contended that the drug product

provides instant acid neutralization, thereby instantly relieving the symptoms that are acid related or mediated (Ref.

The comment argued that the statements "speedy relief" and "fast relief" simply convey, in layman's language, truthful and informative information that the product acts relatively promptly. The comment concluded that there is no basis for prohibiting use of these claims.

In comment 42 of the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204 at 46223), the agency addressed the claim of quicker analgesic benefits for antacid and analgesic combination drug products in a solution dosage form. In that document, the agency concurred with the Internal Analgesic Panel that no well-controlled studies exist to prove that absorption rates will produce therapeutically different results with regard to onset, intensity, or incidence of relief of symptoms. Thus, in the absence of supporting data, such claims were placed in Category III. Further, while the data submitted by the comment (Ref. 1) do indicate that the product provides rapid neutralization of stomach acid, the data do not prove or disprove that rapid acid neutralization will result in clinically significant differences in the onset, intensity, or incidence of relief of symptoms associated with overindulgence of food and/or drink. Therefore, the agency is placing the label claims "fast relief" and "speedy relief" in Category III until further data supporting such claims are provided.

References

(1) OTC Volume 170189, pp. 18–21.
(2) OTC Volume 170189, pp. 17–18.

4. One comment agreed with the Panel's recommendation at 47 FR 43547 that combination products containing antacids and aspirin labeled "for the relief of upset stomach due to overindulgence in the combination of food and drink, when accompanied by a headache or other minor aches and pains" be appropriately buffered so that the final dosage form at least meets the buffering capacity of an antacid final dosage form. The comment also supported the Panel's recommended deletion of the proposed caution against the use of aspirin-containing products in the presence of "gastric distress" for products containing an adequate amount of antacids, and urged the agency to adopt the Panel's recommendation. The comment summarized the Panel's discussion and other data on this subject in support of its contention that highly buffered analgesic-antacid combinations, such as sodium acetylsalicylate and sodium citrate in solution, do not damage the stomach or gastric mucosa, or cause gastrointestinal bleeding (Ref. 1).

In comment 47 of the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204 at 46226), the agency discussed analgesic-antacid labeling claims for aspirin-antacid drug products and stated that such combination drug products for ingestion as a solution should provide at least 5 milliequivalents (mEq) of acid neutralizing capacity as specified in § 331.10(a) of the OTC antacid final monograph (21 CFR part 331). In this document, the agency continues to support that position.

The safety of highly buffered aspirin solutions and aspirin-antacid combinations and the effects of such products on the gastrointestinal tract was also discussed in comment 47 of the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46226). The agency concluded in that document that such combination products should bear warnings against their use by persons who have persistent or recurring stomach problems, such as acid indigestion, or who have ulcers or bleeding problems as stated in the following proposed warning in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (§ 343.50(c)(1)(v)(B)): "Do not take this product if you have stomach problems (such as heartburn, upset stomach, or stomach pain) that persist or recur, or if you have ulcers or bleeding problems, unless directed by a doctor." Because the combination products mentioned by the comment are primarily being handled in the rulemaking for OTC internal analgesic drug products, they would be required to bear this proposed warning.

Reference

(1) Comment No. C0005, Appendix A, Docket No. 82N–0166, Dockets Management Branch.

5. One comment criticized the Panel's reasoning for allowing use for relief of alcoholic hangover symptoms of a combination product that contains active ingredients from at least two of the following three drug categories: Analgesic, antacid, and stimulant. The comment disagreed with the Panel's conclusion that because these ingredients have been reviewed extensively by other Panels and found effective for treating the various symptoms that comprise a hangover, it is unnecessary to require clinical studies to prove the effectiveness of the combination products used to treat hangover (47 FR 43540 at 43551). The comment expressed the belief that, in lieu of clinical studies, and Panel based its recommendation on the fact that over the years people have found it convenient to treat hangover with these combination products.

The comment questioned whether it is correct to classify a product as generally recognized as safe and effective based primarily on the fact that similar products have been used for this purpose for many years. The comment argued that unsafe products such as analgesics containing phenacetin and ineffective products such as hair growing agents were marketed for years and later found to be either unsafe or ineffective. The comment expressed the opinion that the Panel's action with respect to hangover remedies provides evidence that the agency is willing to abandon its legal responsibilities under the OTC drug review because these recommendations are irrational, lack proof of sound scientific evidence, set a precedent for the issuance of further unsound monographs, and allow the marketing of unnecessary and irrational products. The comment concluded that until substantial evidence exists for a given product or ingredient, the agency should not add new products to the OTC market or add new indications on old products.

A second comment recommended that the agency adopt the Panel's determination that the combination of the internal analgesic sodium acetylsalicylate and the antacid sodium citrate in solution is safe and effective in relieving the symptoms of a hangover. The comment expressed the opinion that this determination is fully supported by the scientific literature and years of experience with the product.

The agency believes that the first comment overlooks a number of important considerations in the Panel's evaluation of combination products containing antacids, analgesics, and stimulants to treat hangover symptoms. It was not the Panel's intention to permit random combinations of ingredients in a simple product for a simple indication, but rather to recognize that the term "hangover" referred to a commonly recognized symptom complex that is composed of symptoms for which Category I ingredients that exist in the antacid, internal analgesic, and stimulant monographs can be used. Although acknowledging that no study had been done to determine the relative frequency of hangover symptoms in a

large population, the Panel compiled a list of symptoms that included nausea, heartburn, thirst, tremor, disturbance of equilibrium, fatigue, general aches and pain, headache, dullness and/or depression, and irritability (47 FR 43540 at 43551). The Panel then proposed to allow combination products containing an internal analgesic(s) to treat the headache and general aches, an antacid(s) to treat the gastric distress, and a stimulant (caffeine) to treat the dullness or fatigue. The Panel proposed that any combination of ingredients from two or more of these categories of drugs, was a Category I hangover reliever.

The Panel believed it would be justifiable to combine active ingredients to treat these separate symptoms if the combination met the agency's requirements (47 FR 43540 at 43551). In its "General Guidelines for OTC Drug Combination Products" (Ref. 1), the agency has provided that Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC drug combination policy in all other respects. In this case, the different symptoms treated concurrently are part of the symptom complex. The OTC drug combination policy, as stated in 21 CFR 330.10(a)(4)(iv) of the OTC drug regulations, includes the provisions that combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients, and the combination provides rational concurrent therapy for a significant proportion of the target population.

The agency agrees that a symptom complex known as "hangover" does exist and that its symptoms vary widely from individual to individual. In reviewing the data on hangover symptoms cited by the Panel (Refs. 2 through 6), the agency agrees that many of the symptoms that form the complex are treatable with combination products containing internal analgesic, antacid, or stimulant ingredients. The agency further agrees that certain symptoms of a hangover are relieved by the combination of the internal analgesic sodium acetylsalicylate and the antacid sodium citrate in solution.

The agency notes, however, that in recommending combination products to treat hangover symptoms, the Panel failed to adequately consider that caffeine stimulates gastric secretion of hydrochloric acid (Refs. 7 through 13). The ability of caffeine to significantly increase hydrochloric acid secretion is mentioned in standard medical reference textbooks (Refs. 7 and 8) and was reported by Roth and Ivy (Ref. 13) as early as 1944. McArthur, Hogan, and Isenberg (Ref. 9) undertook a study to determine the effect of nine commonly ingested beverages on gastric acid secretion in humans. Six healthy subjects were each studied on 11 separate days and in random order. Test substances were 3 types of soda water, 3 different brands of instant coffee, tea, milk, and beer. The control was water. The results were considered significantly different for each beverage versus the control ($p<0.05$). The authors stated that this study indicates that each of the beverages tested is a potent stimulus of gastric acid secretion regardless of its caffeine content. Studies by Cohen and Booth (Ref. 10) likewise demonstrated that caffeine stimulates gastric acid secretion and reduces the competence of the lower esophageal sphincter in healthy subjects. Noting that caffeine is a potent stimulant of gastric secretion in man, Roth and Ivy (Ref. 13) conducted experiments to determine the synergistic effect of caffeine upon alcohol. They observed that the gastric secretory response to the combined action of alcohol plus caffeine was an average of 65.9 percent greater than the response produced when alcohol and caffeine were given separately. Further, the response to the combination of alcohol and caffeine was prolonged, lasting approximately 70 minutes longer than that of the individual ingredients.

The Advisory Review Panel on OTC Sedative, Tranquilizer, and Sleep-aid Drug Products (Sleep-aid Panel) noted in its advance notice of proposed rulemaking for OTC nighttime sleep-aid, daytime sedative, and stimulant drug products (December 8, 1975, 40 FR 57292 at 57324 to 57325) that caffeine stimulates gastric secretion in man. While that Panel stated that normal doses of caffeine (i.e., 100 mg) did not seem to cause irritation of the gastrointestinal tract, the agency notes that the target population considered by that Panel in its assessment of the safety and effectiveness of caffeine as an OTC stimulant did not specifically include individuals that already had some degree of stomach or gastrointestinal irritation or upset due to overindulgence in alcohol and/or food. Further, the Sleep-aid Panel did not give any consideration to the safety of caffeine in patients with already high levels of stomach acid.

In view of caffeine's documented effect in stimulating gastric secretions, the agency does not believe that combination products containing both caffeine, which stimulates hydrochloric acid secretion, and an antacid, which reduces the concentration of hydrochloric acid and treats the symptoms associated with high levels of hydrochloric acid, are rational. Therefore, the agency is reversing the Panel's Category I recommendation and is placing in Category II all combination products for the treatment of hangover that contain both an antacid ingredient and caffeine, a stimulant ingredient. The agency is not aware of any marketed OTC drug combination products, other than hangover remedies, that contain both stimulant and antacid ingredients.

Analgesic-antacid combinations are currently included in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products, published in the Federal Register of November 16, 1988 (53 FR 46204). The agency does not see a need to establish a separate monograph for drug products for the relief of hangover symptoms when this indication can readily be incorporated into the rulemaking for OTC internal analgesic, antipyretic, and antirheumatic drug products.

Accordingly, the agency is proposing to eliminate further consideration of drug products for the relief of hangover in this document and is instead proposing elsewhere in this issue of the Federal Register to amend the internal analgesic tentative final monograph in § 343.20 by adding new paragraph (b)(5), to read as follows:

(b) * * *

(5) *Internal analgesic and stimulant combinations.* Any internal analgesic ingredient identified in § 343.10(a) or (b)(1) of this chapter may be combined with any stimulant ingredient identified in § 340.10 of this chapter provided the product bears labeling indications in accordance with § 343.60(b)(6).

The agency is also proposing to amend the labeling for products containing a combination of an internal analgesic and an antacid to include claims for the relief of symptoms of hangover and/or overindulgence in food and drink and to include a warning for products for relief of hangover symptoms in § 343.60 by revising paragraphs (b)(2) and (b)(4) and (c) and by adding new paragraphs (b)(6) and (c)(1), to read as follows:

(b) * * *

(2) *For permitted combinations identified in § 343.20(b)(1).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach,"

or "acid indigestion") (which may be followed by: "and upset stomach associated with" (select one or more of the following, as appropriate: "this symptom," "these symptoms," "hangover," or "overindulgence in food and drink."))

* * * * *

(4) *For permitted combinations identified in § 343.20(b)(3).* The indications are the following: "For the temporary relief of minor aches and pains with" (select one or more of the following: "heartburn," "sour stomach," or "acid indigestion") (which may be followed by: "and upset stomach associated with" (select one or more of the following, as appropriate: "this symptom," "these symptoms," "hangover," or "overindulgence in food and drink")) and "Also may be used for the temporary relief of minor aches and pains alone" (which may be followed by one or more of the following: ("such as associated with" (select one or more of the following: "a cold," "the common cold," "sore throat," "headache," "toothache," "muscular aches," "backache," "the premenstrual and menstrual periods" (which may be followed by "dysmenorrhea"), or "premenstrual and menstrual cramps" (which may be followed by: "(dysmenorrhea)")), ("and for the minor pain from arthritis"), and ("and to reduce fever."))

* * * * *

(6) *For permitted combinations identified in § 343.20(b)(5).* The indications are the following: "For the temporary relief of minor aches and pain associated with a hangover. Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness associated with a hangover."

* * * * *

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warnings(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph.

(1) *For permitted combinations identified in § 343.20(b)(1) and (b)(3) when labeled for the relief of the symptoms of hangover.* "Do not use for more than 2 days for a hangover unless directed by a doctor."

(2) [Reserved]

The agency is further proposing elsewhere in this issue of the **Federal Register** to amend the OTC stimulant final monograph by adding a new section § 340.20 to subpart B to include combinations of stimulant and nonstimulant active ingredients, to read as follows:

Section 340.20 *Permitted combinations of active ingredients.*

The following combinations are permitted provided each active ingredient is present within the established dosage limits and the product is labeled in accordance with § 340.60.

(a) *Combinations containing a stimulant active ingredient and an internal analgesic active ingredient(s).* (See § 343.20(b)(5) of this chapter.)

(b) [Reserved]

The agency is also proposing to add new § 340.60 to supart C, to read as follows:

Section 340.60 *Labeling of permitted combinations of active ingredients.*

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. Other truthful and nonmisleading statements describing only the indications for use that have been established and listed in this paragraph may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For permitted combinations containing a stimulant and an internal analgesic active ingredient identified in § 340.20(a).* The indications in § 343.60(b)(6) of this chapter should be used.

(2) [Reserved]

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph.

For permitted combinations containing any stimulant ingredient identified in § 340.20. The following warning should be used instead of the warnings in §§ 340.50(c)(2) and 343.50(c)(1) of this chapter: "For occasional use only. Do not use for more than 2 days for a hangover unless directed by a doctor. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a" (select one of the following: "physician" or "doctor").

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product:

(1) May not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC drug monograph(s), and

(2) May not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient.

The agency is further proposing elsewhere in this issue of the **Federal Register** to amend § 331.30 of the OTC antacid monograph by revising paragraph (b), to read as follows:

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For the relief of" (select any or all of the following: "heartburn," "sour stomach," and/or "acid indigestion") (which may be followed by the statement: "and upset stomach associated with" (select one or more of the following, as appropriate "this symptom," "these symptoms," or "overindulgence in food and drink.") Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

In proposing the above labeling the agency hopes to eliminate consideration of overlapping claims for the same ingredients subject to different OTC drug monographs and, at the same time, limit combinations to those which have been proven scientifically sound and justified.

References

(1) Food and Drug Administration "General Guidelines for OTC Drug Combination Products, September 1978, "Docket No. 78D–0322, Dockets Management Branch.

(2) Collins, W. E., "Performance Effects of Alcohol Intoxication and Hangover at Ground Level and at Simulated Altitude," Aviation Space and Environmental Medicine, 51:327–335, 1980.

(3) Anylian, G. H., J. Dorn, and J. Swerdlow, "The Manifestation, Aetiology and Assessment of Ethanol-Induced Hangover," South African Medical Journal, 54:193–198, 1978.

(4) Khan, M. A., K. Jensen, and H. J. Krough, "Alcohol-Induced Hangover: A Double-Blind Comparison of Pyritinol and Placebo in Preventing Hangover Symptoms," Quarterly Journal of Studies on Alcohol, 34:1195–1201, 1973.

(5) Chapman, L. F., "Experimental Induction of Hangover," Quarterly Journal of

Studies on Alcohol, Supplement No. 5:67–86, May 1970.

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(7) Rall, T. W., "Drugs Used in the Treatment of Asthma," in "The Pharmacological Basis of Therapeutics," 8th ed., edited by A. G. Gilman, et al., Pergamon Press, New York, p. 623, 1990.

(8) Ivey, K. J., and J. L. A. Roth, "Drug and Chemical-Induced Injuries of the Stomach," Chapter 64 in "Bockus Gastroenterology," 4th ed., Edited by J. E. Berk, W. B. Saunders Co., Philadelphia, pp. 975 and 995, 1985.

(9) McArthur, K., D. Hogan, and J. L. Isenberg, "Relative Stimulatory Effects of Commonly Ingested Beverages on Gastric Acid Secretion in Humans," Gastroenterology, 83:199–203, 1982.

(10) Cohen, S., and G. H. Booth, Jr., "Gastric Acid Secretion and Lower-Esophageal-Sphincter Pressure in Response to Coffee and Caffeine," The New England Journal of Medicine, 293:897–899, 1975.

(11) Friedman, G. D., A. B. Siegelaub, and C. C. Seltzer, "Cigarettes, Alcohol, Coffee and Peptic Ulcer," The New England Journal of Medicine, 290:469–473, 1974.

(12) Debas, H. T., et al., "Caffeine-Stimulated Acid and Pepsin Secretion: Dose-Response Studies," Scandinavian Journal of Gastroenterology, 6:453–457, 1971.

(13) Roth, J.A., and A.C. Ivy, "The Synergistic Effect of Caffeine Upon Histamine in Relation to Gastric Secretion," American Journal of Physiology, 142:107–113, 1944.

6. One comment supported the Panel's recommendation for modified warnings for hangover relief drug products containing internal analgesic ingredients. Specifically, the comment agreed with the Panel that the 10-day limitation on use of the drug (see recommended warning for OTC internal analgesic drug products in § 343.50(c)(1)(i) at 42 FR 35493) and that the caution regarding use of an internal analgesic with prescription drugs taken for diabetes, gout, and arthritis (see recommended warning for OTC internal analgesic drug products in § 343.50(c)(3)(v) at 42 FR 35493) should be deleted. The comment supported the Panel's reasoning that such modifications of the warnings recommended for OTC internal analgesic drug products were appropriate because hangover is considered an acute, self-limiting condition that does not require warnings applicable to products subject to more prolonged use. The comment also supported the Panel's recommendation to delete, as too vague, the words "or other symptoms" from the warning for OTC internal analgesic drug products (proposed in § 343.50(c)(3)(ii) at 42 FR 35493), that states "Stop taking this product if ringing in the ears or other symptoms occur."

The agency disagrees with the Panel's recommendations for deleting or modifying the warnings applicable to internal analgesic ingredients contained in products for the treatment of hangover. While hangover is generally an acute self-limiting condition, the symptom complex can be experienced for periods of several days, either as a result of excessive and physically harmful consumption of alcoholic beverages or as a result of the consumption of alcohol aggravating some other disease or condition. If the condition persists for more than 2 days, the individual should seek medical guidance and not continue to rely on a hangover remedy for symptomatic relief.

As discussed in comment 5, the agency is not including combinations of products for the relief of hangover in this rulemaking, but elsewhere in this issue of the **Federal Register** the agency is amending the tentative final monograph for OTC internal analgesic drug products to include internal analgesic/antacid and internal analgesic/stimulant combinations for the relief of hangover symptoms. Accordingly, the agency concludes that combination products for relief of hangover symptoms that contain an internal analgesic ingredient should bear the applicable warnings required under § 343.50 of the internal analgesic tentative final monograph, and the interaction warning concerning use with prescription drugs used to treat gout, diabetes, and arthritis.

With regard to the 10-day limitation on use of internal analgesics, the agency notes that when the limitation for the use of the individual ingredients in a combination drug product differ, the labeling for the combination product may not exceed any maximum limit established for the individual ingredients in the applicable OTC drug monographs. Antacids have a 2-week limitation of use (21 CFR 331.30(c)(1)), internal analgesics have a 10-day limitation of use (proposed 21 CFR 343.50(c)(1); 53 FR 46204 at 46256), and stimulants, although recommended only for occasional use, have no established limitation of use (21 CFR Part 340). Therefore, any combination product for relief of hangover symptoms containing an internal analgesic would be limited to use for no more than 10 days. However, as discussed above, the agency believes that individuals who require the use of a hangover relief product for more than 2 days should seek medical guidance. Therefore, the agency proposes to limit the use of any OTC hangover relief drug product to 2 days unless directed by a doctor. The agency is proposing to amend § 343.60 of the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products by adding new paragraph (c)(1), to read as follows:

(1) *For permitted combinations identified in § 343.20(b)(1) and (3) when labeled for the relief of the symptoms of hangover.* "Do not use for more than 2 days for a hangover unless directed by a doctor."

The agency is also proposing to amend § 340.60 of the final monograph for OTC stimulant drug products by adding new paragraph (c), to read as follows:

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. The following warning should be used for permitted combinations containing any stimulant ingredient identified in § 340.20 instead of the warnings in §§ 340.50(c)(2) and 343.50(c)(1) of this chapter: "For occasional use only. Do not use for more than 2 days for a hangover unless directed by a doctor. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a" (select one of the following: "physician" or "doctor").

The agency points out that the term "other symptoms," was deleted, as requested by the comment, from the warning in § 343.50(c)(3)(ii) in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products which was published in the **Federal Register** of November 16, 1988 (53 FR 46204 at 46257).

7. One comment concurred with the Panel that no ingredient has been demonstrated to be both safe and effective to prevent or reduce inebriation. However, the comment expressed concern that since the advance notice of proposed rulemaking was published, numerous sobering agents have been advertised and readied for marketing. According to the comment, many of these products have sought to avoid FDA's OTC drug approval procedures by claiming that they are food supplements. The comment was also greatly concerned that these products would be misused to "make drinking safer" or "to control drunken driving." The comment added that, before such products are allowed to be marketed, evidence must be presented that demonstrates benefits for all potential users of the product, e.g., men and women, all ages (over 16), light to heavy drinkers (including alcoholics), and that includes test-simulating real-

life activities such as driving. The comment stated that unless a product is shown to eliminate all sensory and cognitive impairment resulting from alcohol ingestion, FDA should reject any use of the term "sober" to describe or name such a product. The comment stated that, if such products were approved, their labeling should warn against reliance on the product (1) to improve driving capabilities after drinking or (2) to increase one's alcohol consumption. The comment concluded that any approved labeling should not mislead drinking consumers into believing that drinking and driving are somehow compatible or that sustained, excessive drinking does not pose substantial health, social, and safety risks.

The agency shares the comment's concerns. In the **Federal Register** of July 19, 1983 (48 FR 32872), FDA declared any such product to be a new drug and, as such, it must be the subject of an approved NDA before marketing occurs. This notice stated that products intended to minimize or prevent inebriation may present a health hazard, particularly when motorists rely on unsubstantiated claims that a product will prevent or minimize an inebriated state, and such products could give persons who consume alcoholic beverages and then drive a motor vehicle a false sense of security. Therefore, all testing and labeling for any such product will have to be approved by the agency before such a product may be legally marketed. No such drug products are currently marketed, and the agency is not aware of any product intended to prevent or reduce inebriation being marketed as a food supplement.

II. The Agency's Tentative Conclusions on the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. Summary of Ingredient Categories

The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made some changes in the categorization of active ingredients recommended by the Panel for drug products for relief of symptoms associated with overindulgence in food and drink. In addition, as discussed in the comments above, the agency is limiting the rulemaking for OTC overindulgence drug products to only those ingredients that have not been adequately covered by other OTC drug rulemakings for similar claims related to relief of symptoms of upset stomach associated with overindulgence in food and drink or hangover. As a convenience to the reader, the following list is included as a summary of the categorization of overindulgence active ingredients recommended by the Panel and the proposed categorization by the agency. Where the ingredient has been classified in another rulemaking, that rulemaking and the classification therein is stated.

CATEGORIZATION OF INGREDIENTS

Active ingredients	Panel				Agency
	Overindulgence	[1] Hangover reliever	Hangover minimizer	Inebriation minimizer	
Acetaminophen		I			Internal analgesic (I).
Aluminum hydroxide		I			Antacid (I).
Aluminum hydroxide gel		I			Antacid (I).
Aspirin		I			Internal analgesic (I).
Bismuth subsalicylate	I				I.
Caffeine		I			Stimulant (I).
Charcoal, activated			III		III.
Fructose				III	[2] II (New Drug).
Magnesium carbonate		I			Antacid (I).
Magnesium trisilicate		I			Antacid (I).
Sodium acetylsalicylate in solution		I			Internal analgesic (I).
Sodium citrate in solution	I	I			Antacid (I).

[1] The Panel classified these ingredients in Category I for hangover relief only when used in combination as provided in parts 331, 340, and 343.
[2] All products intended to prevent or minimize inebriation were classified as new drugs in the Federal Register of July 19, 1983 (48 FR 32872).

2. Testing of Category II and Category III Conditions

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any overindulgence ingredient or condition included in this review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows:

(1) The agency is limiting the rulemaking for OTC overindulgence drug products to include only those ingredients that have not been adequately covered by other OTC drug rulemakings that address similar claims related to relief of symptoms of hangover or overindulgence in food and drink. (See comments 1 and 5, above, and section II. A. 1.)

(2) The agency has revised the phrase "due to overindulgence in the combination of alcohol and food" recommended by the Panel in the proposed headings for § 357.910 and § 357.950 to read "due to overindulgence in food and drink." The use of the word "combination" is redundant and unnecessary.

(3) The agency is proposing a new statement of identity "upset stomach reliever," for products labeled for the relief of overindulgence in food and drink. (See comment 1.)

(4) The agency is not including combinations containing bismuth subsalicylate and nonsalicylate analgesic active ingredients labeled for the relief of symptoms of upset stomach due to overindulgence in food and drink in this tentative final monograph. While such combinations were recommended as Category I in the advance notice of proposed rulemaking (47 FR 43540 at 43558), the agency is unaware of any data supporting the safety and effectiveness of such combinations. Further, the agency is unaware that such combinations have ever been marketed. Because no combinations of active ingredients for relief of symptoms of upset stomach due to overindulgence in food and drink are currently included in this rulemaking, the agency is not including the Panel's recommended § 357.920 *Permitted combinations of active ingredients* in the tentative final monograph.

(5) The agency is adding, as § 357.950(c)(2), the warning proposed in § 343.50(c)(1)(vi) of the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204 at 46256) "Do not take this product if you are allergic to salicylates (including aspirin) unless directed by a doctor."

(6) The agency is adding a warning appearing as § 357.950(c)(3) "Do not use for more than 2 days unless directed by a doctor" to reflect safety considerations and the dose limitation for bismuth subsalicylate-containing products addressed in the tentative final monograph for OTC antidiarrheal drug products (51 FR 16138 at 16143 and 16149).

The agency is also modifying the Panel's warning recommended in § 357.950(c)(1)(ii) for products containing bismuth subsalicylate labeled for the relief of symptoms of upset stomach due to overindulgence in food and drink to conform to a similar warning the agency proposed for other salicylates in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products in § 343.50(c)(1)(v)(C) (53 FR 46204 at 46256). The warning, appearing as § 357.950(c)(4) in this tentative final monograph, reads as follows: "*Drug Interaction Precaution:* Do not take this product if you are taking a prescription drug for anti coagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor."

(7) The agency is combining several indications statements recommended by the Panel in § 357.956(b) for drug products to minimize hangover symptoms and is slightly revising the directions paragraph for bismuth subsalicylate labeled for relief of symptoms of upset stomach due to overindulgence in food and drink in § 357.950(d) to conform with the format of other recently published tentative final monographs.

(8) In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for physician in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC overindulgence drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC overindulgence drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC overindulgence drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by April 22, 1992. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before April 22, 1992, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before April 22, 1992. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before December 24, 1992, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before February 24, 1993. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (address above). Received data and comments may also be seen in the office above

between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on February 24, 1993. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 357

Labeling, Over-the-counter drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 357 be amended as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 357 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. A new Subpart J is added to Part 57 to read as follows:

Subpart J—Orally Administered Drug Products for Relief of Symptoms Associated with Overindulgence in Food and Drink

Sec.

Subpart J—Orally Administered Drug Products for Relief of Symptoms Associated with Overindulgence in Food and Drink

§ 357.901 Scope.

(a) An over-the-counter drug product for the relief of symptoms of upset stomach due to overindulgence in food and drink or to minimize hangover symptoms, in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 357.903 Definitions.

As used in this subpart:

(a) *Upset stomach due to overindulgence in food and drink.* A condition which occurs as a result of overindulgence in food and drink and consists of a group of symptoms which includes heartburn, fullness, and nausea.

(b) *Hangover.* A condition consisting of a complex of symptoms involving the gastrointestinal, neurologic, and metabolic system that follows recent acute excessive alcohol ingestion. The symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness, and/or depression or irritability.

§ 357.910 Active ingredients for the relief of symptoms of upset stomach due to overindulgence in food and drink.

The active ingredient of the product is bismuth subsalicylate when used within the dosage limits established in § 357.950(d).

§ 357.916 Active ingredients to minimize hangover symptoms. [Reserved]

§ 357.950 Labeling of drug products for the relief of symptoms of upset stomach due to overindulgence in food and drink.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "upset stomach reliever."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act:

(1) "For the relief of upset stomach due to overindulgence in food and drink."

(2) "For the relief of upset stomach associated with" (select one or more of the following: "nausea," "heartburn," and "fullness") "due to overindulgence in food and drink."

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

(1) "This product contains salicylate. If taken with other salicylate-containing preparations (such as aspirin) and ringing in the ears occurs, discontinue use."

(2) "Do not take this product if you are allergic to salicylates (including aspirin) unless directed by a doctor."

(3) "Do not use for more than 2 days unless directed by a doctor."

(4) "*Drug Interaction Precaution.* Do not take this product if you are taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout, or arthritis unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions" for products containing bismuth subsalicylate identified in § 357.910. Adults and children 12 years of age and over: oral dosage is 0.525 gram every ½ to 1 hour, as required, not to exceed 4.2 grams or 8 doses in 24 hours. Children under 12: consult a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 357.956 Labeling of drug products to minimize hangover symptoms.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "hangover minimizer."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: (Select one of the following: "To minimize," "For minimizing," or "Helps to minimize") "the symptoms of a hangover caused by alcoholic beverages." Other truthful and nonmisleading statements, describing only the indications for use that have been established in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or deliver for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

Dated: November 1, 1991.

Michael R. Taylor,

Deputy Commissioner for Policy

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