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21 CFR Part 340

Stimulant Drug Products for Over-the-Counter Human Use; Final Monograph; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 340

[Docket No. 75N-0244]

Stimulant Drug Products for Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) stimulant drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on stimulant drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: March 1, 1989.

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 8, 1975 (40 FR 57292), 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 stimulant drug products, together with the recommendations of the Advisory Review Panel on OTC Sedative, tranquilizer, and Sleep-aid Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by March 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by April 8, 1976.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC stimulant drug products was published in the **Federal Register** of June 13, 1978 (43 FR 25544). Interested persons were invited to file by August 14, 1978, written objections and/or requests for an oral hearing before the Commissioner of Food and Drugs regarding the proposal. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC stimulant drug products.

In the **Federal Register** of October 26, 1979 (44 FR 61610), the agency published a notice reopening the administrative record for OTC stimulant drug products from October 26, 1979 to March 26, 1980 to permit manufacturers to submit, prior to the establishment of a final monograph, new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Interested persons were invited to submit comments on the new data on or before May 27, 1980. Data and information received after the administrative record was reopened are on display in the Dockets Management Branch.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18399), the agency advised that it had also reopened the administrative record for OTC stimulant drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch during the period from August 14, 1978 to October 26, 1979. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a final monograph.

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 is no longer using 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 is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

The agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after March 1, 1989, no OTC drug products 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 products 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.

In the tentative final monograph for OTC stimulant drug products, the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling

and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is providing an effective date of 12 months after the date of publication of the final monograph in the **Federal Register**.

In response to the proposed rule on OTC stimulant drug products, three consumers, two consumer groups, three drug manufacturers, one soft-drink manufacturer, one drug manufacturer association, and one consultant representing a drug manufacturer submitted comments. Requests for oral hearing before the Commissioner were also received on three different issues. Copies of the comments and the hearing requests received are on public display in the Dockets Management Branch. Any addition information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final monograph, the agency has considered all objections, requests for oral hearing, and the changes in the procedural regulations. In those cases where the agency has agreed with submitted objections and has revised the final monograph accordingly, the Commissioner concludes that any accompanying requests for hearing are moot. Therefore, such hearing requests are not discussed in the following responses to comments.

One comment requested hearings on several aspects of the rule if the Commissioner, in making his decisions, relied upon evidence that was not in the public domain. The Commissioner advises that the agency's decisions in this rulemaking have been based entirely on the administrative record, publicly available in the Dockets Management Branch. Therefore, the Commissioner concludes that the comment has not requested hearings on those issues. The Commissioner also concludes that, even if the comment had not conditioned its requests on the existence of unknown evidence, hearings on those issues would not be warranted.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments on Stimulant Drug Products

1. One comment concurred with the agency's recommendations for establishing conditions for the safety and labeling of OTC stimulant drugs.

2. One comment contended that the Commissioner's conclusion in the tentative final monograph that flavors and sugars or their substitutes should not be included in stimulant drug products containing caffeine was unreasonable, arbitrary, capricious, and not supported by substantial evidence. The comment argued that there was no showing on the part of the agency that lesser measures short of banning flavors, such as safety caps or limitation of the number of caffeine tablets in a package, could not provide the protection desired against accidental ingestion by children. Another comment argued that there are numerous OTC drug products on the market that contain flavors, that no factual showing has been made that the inclusion of flavors in stimulant drug products encourages their ingestion by children, and that no reason is presented by the agency as to why stimulant drug products should be treated differently than other OTC drug products; that chewable flavored caffeine tablets would be convenient when water is not available; that banning flavors in caffeine tablets would discourage adult use because caffeine tablets would be bitter to the taste and that sugars and flavors are pharmaceutical necessities and meet the criteria for safe and suitable inactive ingredients.

Based on the list of food ingredients generally recognized as safe (the GRAS list), or approved food additives, codified in 21 CFR Parts 172, 182, and 184, the agency agrees that sugars and flavors are safe and suitable inactive ingredients that may be added to OTC drug products as specified in 21 CFR 330.1(e). In the tentative final monograph (43 FR 25599), the Commissioner strongly recommended that these substances not be included in OTC stimulant drug products. This recommendation appeared only in the preamble and was not included in the tentative final monograph. No such restriction appears in this final monograph. Thus, manufacturers have the option to decide whether or not to add flavors and sweeteners to their OTC stimulant drug products and the responsibility to assure that such inactive ingredients meet the criteria set forth in § 330.1(e).

3. One comment urged that FDA should immediately mount an educational campaign to warn women who are pregnant, or who expect to become pregnant, to avoid all caffeine-containing drug products as well as other products that contain caffeine, such as coffee and tea.

FDA has carried out a number of educational activities related to caffeine, whether used as a drug or in food products such as coffee and tea. These activities have included the establishment in 1980 of a Caffeine Education Working Group to further the agency's educational effort to increase public and professional awareness of the possible link between caffeine consumption and birth defects. Members of this group were policy-level executives from FDA's Center for Food Safety and Applied Nutrition, Center for Drugs and Biologics, Office of Legislation and Information, Office of Consumer Affairs, and others. The group reviewed issuance of consumer memos; news releases and talk papers to the press, television, and radio; and articles for consumer-related journals, such as the *FDA Consumer*. Significant educational activities included the widely distributed consumer memo, entitled "Caffeine and Pregnancy" (1981); a radio spot announcement, entitled "Caffeine and Pregnancy" (October 1980); and a statement by Jere E. Goyan, then Commissioner of Food and Drugs, summarizing the agency's current caffeine recommendations (September 1980) (Ref. 1). An article on caffeine appeared in the November 1980 *FDA Drug Bulletin*, advising practitioners (Ref. 2). In May 1981, the Center for Food Safety and Applied Nutrition issued a report of a 1980 multipurpose survey conducted to determine public awareness of the potential dangers of consumption of alcohol and caffeine by pregnant women (Ref. 3). In addition, the FDA Office of Consumer Affairs *Consumer Update* for April 1982 included an article dealing with caffeine and alcohol use in pregnancy. The caffeine situation was updated in the March 1984 issued of *FDA Consumer* with the article "The Lastest Caffeine Scoreboard" (Ref. 4), which was converted into a newspaper column (Ref. 5) and also distributed in Spanish (Ref. 6). The most recent FDA update on caffeine appeared in the December 1987/January 1988 issue of the *FDA Consumer* (Ref. 7). A detailed list of the agency's educational activities on caffeine has been placed on file in the Dockets Management Branch (Ref. 1). Thus, it can be seen that the agency

has implemented an educational campaign to inform the American public about the status of caffeine. (See also comment 7 below.)

References

(1) "Accomplished Caffeine Education Activities" and "Planned Caffeine Education Activities," June 1981, OTC Volume 05AFM, Docket No. 75N-0244, Dockets Management Branch.

(2) "Caffeine and Pregnancy," *FDA Drug Bulletin*, 10:19–20, 1980.

(3) Heimbach, J.T., "Alcohol, Caffeine, and Pregnancy: The Public View," Report issued by the Division of Consumer Affairs, Bureau of Foods, May 1981, OTC Volume 05AFM, Dockets Management Branch.

(4) Lecos, C., "The Lastest Caffeine Scorecard," *FDA Consumer*, 18:14–15, 1984, OTC Volume 05AFM, Dockets Management Branch.

(5) "Caffeine," draft of newspaper article, Communications Staff, Food and Drug Administration, April 1984, OTC Volume 05AFM, Dockets Management Branch.

(6) "Cafeina," draft of newspaper article, Communications Staff, Food and Drug Administration, April 1984, OTC Volume 05AFM, Dockets Management Branch.

(7) Lecos, C.W., "Caffeine Jitters: Some Safety Questions Remain," *FDA Consumer*, 21:22–27, 1987 OTC Volume 05AFM, Dockets Management Branch.

4. One comment urged the government to examine further the teratogenic potential of caffeine in experimental animals. Two comments urged FDA to include in the labeling of OTC stimulant drug products containing caffeine a warning to pregnant women not to consume these products. In support of this recommendation, one comment submitted a selected bibliography on human and animal studies in which caffeine was reported to be associated with birth defects (Ref.1) and a published journal article reporting a limited human epidemiology study on human birth defects and pregnancy complications associated with the consumption of coffee by pregnant women (Ref. 2).

In the proposed rule for OTC stimulant drug products published in the **Federal Register** of June 13, 1978, the agency extensively discussed the teratogenicity of caffeine (43 FR 25563) and will not repeat that discussion here. In the **Federal Register** of October 21, 1980 (45 FR 69817), the agency announced that it had reviewed the human and animal studies reported in the literature and found that these studies did not demonstrate a clear association between caffeine consumption during pregnancy and human birth defects. The agency also noted that the authors of the journal article cited by one of the comments subsequently acknowledged that the data they obtained were preliminary in nature and that further epidemiology studies were needed to assess birth defects as related to caffeine and coffee consumption in humans (45 FR 69826). In a retrospective study of over 12,000 women, no association was found between coffee consumption and adverse outcomes of pregnancy (Ref. 3). In another case-control study of more than 2,000 malformed infants, six specific congenital malformations were evaluated in relation to ingestion by the mothers of caffeine from tea, coffee, and cola beverage during pregnancy. The results of this study did not reveal any relationship between caffeine intake during pregnancy and birth defects in human infants (Ref. 4). A large number of studies have been completed and submitted to FDA. The data assembled since 1980 include studies on teratology, reproduction, behavior, carcinogenicity, and cardiovascular effects. Recently the agency announced the results of its review of these data in discussing the safety of added caffeine in nonalcoholic carbonated beverages. (See the **Federal Register** of May 20, 1987; 52 FR 18923.)

In the **Federal Register** of December 3, 1982 (47 FR 54570), the agency published a final rule requiring the following warning in the labeling of all OTC drug products that are intended for systemic absorption: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." This general warning is required for all OTC drug products, including stimulant drug products containing caffeine, that are intended for systemic absorption into the body. (See 21 CFR 201.63(a).)

The agency recognizes that caffeine is a broad issue involving foods and food additives as well as drugs. Consequently, should additional data and information demonstrate and need for significant changes in the regulation of caffeine as an OTC stimulant drug, the agency will amend the final monograph at that time.

References

(1) Comment No. 0B0006, Docket No. 75N-0244, Dockets Management Branch.

(2) Borlee, L., et al., "Coffee, Risk Factor During Pregnancy?" *Louvain Medical*, 97:279–284, 1978.

(3) Linn, S., et al., "No Association Between Coffee Consumption and Adverse Outcomes of Pregnancy," *New England Journal of Medicine*, 306:141–145, 1982.

(4) Rosenberg, L., et al., "Selected Birth Defects in Relation to Caffeine-Containing Beverages," *Journal of the American Medical Association*, 247:1429–1432, 1982.

B. Comments of Labeling of Stimulant Drug Products

5. One comment contended that FDA does not have the authority to legislate the exact wording of OTC drug labeling claims. The comment contended that such a policy is overly restrictive, lacks supporting evidence, and constitutes a prior restraint on First Amendment rights. The comment concluded that to ban alternative truthful language is unjustified. The comment also requested a hearing on this issue.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph where exact language has been established and identified by quotation marks in an applicable monograph or other regulation, e.g. 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the final rule revising the labeling policy.

6. One comment objected to the agency's denial of a prophylactic indication for OTC stimulant drug products, contending that no rational basis was given for the denial of this claim. The comment argued that the agency did not satisfactorily explain its distinction between the consumers' supposed inability to anticipate initially the need for a prophylactic dose of a stimulant (e.g., in situations where they had previously experienced highway hypnosis, boredom, or mental dullness) and their acknowledged ability to recognize, after the onset of symptoms of fatigue, the need for a repeated dose to ward off the recurrence of such

problems. The comment further contended that a prophylactic labeling claim is appropriate because it would allow consumers to use a stimulant drug product to prevent mental fatigue rather than to counteract it after it has occurred. For this purpose, the comment proposed labeling claims such as "to help ward off drowsiness (dullness); (mental fatigue), when expected to occur," and contended that the phrase "when expected to occur" will inform consumers that the prophylactic use is for occasional use only. The comment requested a hearing if the agency, in refusing to approve a claim for prophylactic use, based its action on any facts of which the comment is unaware.

The agency disagrees with the comment that no rational basis was given for the denial of a prophylactic claim. The agency's position on the prophylactic use of OTC stimulant drugs was set forth in comment 95 of the tentative final monograph at 43 FR 25561. In that document, the agency affirmed the Panel's view that OTC stimulant drugs could be used safely and effectively to restore mental alertness or wakefulness when fatigue or drowsiness was being experienced, but that there was no basis for recommending general prophylactic use.

Caffeine is the only ingredient included in the stimulant final monograph. The Panel noted that chronic ingestion of caffeine in larger than recommended doses can lead to "habituation," which is a mild form of addition (40 FR 57324; December 8, 1975). The Panel therefore recommended that caffeine-containing stimulant drug products be used only occasionally and included the statement "for occasional use only" in a recommended warning. The agency concurs, and this statement is included in the warning in § 340.50(c)(2) of the final monograph. A drug that is limited to occasional use should be taken for a real and present need, not for a need that is not certain to occur. The agency disagrees with the comment that the phrase "when expected to occur" would indicate to consumers that prophylactic use is for occasional use only because an individual may expect fatigue to occur daily. Further, the agency finds no rationale for prophylactic use of caffeine in view of the action of this drug to restore alertness within a reasonable period of time once fatigue or drowsiness has occurred. The agency concludes that a hearing on this issue is not warranted because its action in denying the suggested labeling claim is not based on any facts of which the comment is unaware.

7. One comment objected to the following warning in proposed § 340.50(c)(1): "Caution: Do not exceed recommended dose since side effects may occur which include increased nervousness, anxiety, irritability, difficulty in falling asleep, and occasionally disturbances in heart rate and rhythm called palpitations." The comment stated that the proposed warning is too wordy, that the terms "nervousness" and "anxiety" are perceived by the lay public as being largely synonymous and therefore are redundant, and that the phrase "occasional disturbances in heart rate and rhythm called palpitations" would be unnecessarily frightening to consumers. The comment argued that changes in heart rate are harmless, transitory, occur rarely, and would be accompanied, in any event, by nervousness or irritability about which consumers are already informed. The comment requested that the proposed warning be deleted from the monograph.

Two comments requested changes in the warning statement in proposed § 340.50(c)(4): For products containing caffeine: "The recommended dose of this product contains about as much caffeine as a cup of coffee. Take this product with caution while taking caffeine-containing beverages such as coffee, tea, or cola drinks because large doses of caffeine may cause side effects as cautioned elsewhere on the label." One of these comments argued that many consumers customarily drink more than one cup of coffee at a time and that a caution implying that as little as two cups of coffee may cause occasional disturbances in heart rate and rhythm, increased nervousness, excitability, and irritability would seriously detract from the credibility of all warning statements. The comment recommended that the warning be revised to read: "Do not exceed recommended dose."

The other comment contended that the warning was misleading because it mentioned only tea, coffee, and cola drinks without mentioning the amount of caffeine in each. The comment stated that an 8-ounce serving of a cola drink generally contains less than half the amount of caffeine found in an 8-ounce serving of coffee or tea. The comment also contended that the listing was incomplete because there are other beverages, foods, and medications that contain caffeine. The comment further noted the relatively short half-life of caffeine and stated that exceeding the recommended dose of caffeine would only pose a danger when other sources of caffeine would be ingested together with, or within several hours of, the caffeine drug product. The comment requested that the proposed warning be changed to read "Contains caffeine. Do not take this product with large amounts of caffeine-containing foods, beverages, or medication because large doses of caffeine may cause side effects as cautioned elsewhere on the label."

The agency does not believe that the warning statements in proposed § 340.50(c)(1) should be deleted or that the warning statement in proposed § 340.50(c)(4) is misleading. The agency believes it is important for consumers to know that caffeine drug products should not be taken along with large amounts of other caffeine-containing products because side effects will occur when too much caffeine is ingested at one time. The agency also believes it is important for consumers to know what these side effects are, but believes it is possible to state them more clearly and succinctly than they are stated in the proposed warning. The terms "anxiety" and "nervousness" are sufficiently synonymous in the minds of consumers to be adequately covered by the term "nervousness;" therefore, "anxiety" is deleted from the list of side effects. The phrase "disturbances in heart rate and rhythm called palpitations" is changed to "rapid heart beat" because the agency believes this language is more readily understandable and potentially less disturbing to consumers. The agency is also combining the warning statement in § 340.50(c) (1) and (4) into a revised warning under § 340.50(c)(1) that reads as follows: "The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat."

In addition, the agency believes that consumers should be warned that caffeine drug products are not intended for use as a substitute for sleep, and proposed § 340.50(c)(2) is accordingly revised to read: "For occasional use only. 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"). As previously proposed, this warning advised consumers to consult a doctor "if fatigue or drowsiness persists continuously for more than 2 weeks." The agency finds no basis for specifying a time period of more than 2 weeks in this instance and concludes that it is

more helpful to advise consumers to consult a doctor if fatigue or drowsiness persists or continues to recur.

C. Comments on Combination Drug Products

8. One comment objected to the agency's proposed Category II classification of ammonium chloride for use as a stimulant both as a single active ingredient and in combination with caffeine as discussed in comments 93 and 94 of the tentative final monograph (43 FR 25561). The comment pointed out that its submission to the Panel had been made in response to the request for data on OTC drug products containing stimulants and that its product contained caffeine as a stimulant and ammonium chloride as a diuretic with the claim "helps relieve premenstrual symptoms: swelling, weight gain, and fatigue." The comment stated that the fatigue part of the claim was based on the caffeine component only, and that no stimulant action was attributed to the ammonium chloride. The comment requested that classification of the combination drug product, as labeled, be deferred until the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel) had completed its review of ammonium chloride as a diuretic agent.

The agency concurs. After reviewing the comment's original submission (Ref. 1) again, the agency accepts the comment's explanation that ammonium chloride was not intended for use as a stimulant drug ingredient, but rather as a diuretic, and therefore finds no need to classify ammonium chloride in Category II for use as a stimulant. Further, since the tentative final monograph was published, the Miscellaneous Internal Panel has reviewed OCT orally administered menstrual drug products. Because the product in question is labeled for use in relieving premenstrual symptoms, the agency deferred this combination of ingredients to the Miscellaneous Internal Panel for review. That Panel's recommendations were included in the advance notice of proposed rulemaking for OTC menstrual drug products, published in the **Federal Register** of December 7, 1982 (47 FR 55076). The agency will state its position on the combination of ammonium chloride and caffeine for relief of premenstrual symptoms in the tentative final monograph for OTC menstrual drug products, to be published in a future issue of the **Federal Register**.

Reference

(1) OTC Volume 180009.

II. Summary of Significant Changes From the Proposed Rule

1. The agency has redesignated proposed Subpart D as Subpart C and has placed the labeling sections of the monograph in Subpart C.

2. Based on the definition of a stimulant in § 340.3 and the indications in § 340.50(b) which state that a stimulant drug product helps restore mental alertness, the agency is providing for an alternate statement of identity, i.e., "alertness aid," for these products. This term is reflective of the intended use of the products to which it applies in the same way as are other statements of identity developed in the OTC drug review, such as "digestive aid," "first aid antibiotic," and "nighttime sleep-aid." Accordingly, § 340.50(a) in this final monograph reads "*Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an 'alertness aid' or a 'stimulant'."

3. 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 regulations will give manufacturers the option of using either the word "Physician" or the word "doctor." This final monograph includes that option.

4. The agency is combining proposed § 340.50(c) (1) and (4) in § 340.50(c)(1) to read as follows: "The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat." The agency is also revising the warning in § 340.50(c)(2) to read as follows: "For occasional use only. 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"). (See comment 7 above.)

5. The agency is evaluating the combination of ammonium chloride and caffeine used for relieving symptoms of premenstrual tension in the rulemaking for OTC menstrual drug products. Because ammonium chloride is claimed to act as a diuretic and not a stimulant in this instance, the agency is withdrawing its proposed Category II classification of this ingredient for use as a stimulant. (See comment 8 above.)

III. The Agency's Final Conclusions on OTC Stimulant Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC stimulant drug products are generally recognized as safe and effective and not misbranded. specifically, the agency has determined that the only ingredient that meets monograph conditions is caffeine. All other ingredients considered in this rulemaking, i.e., ammonium chloride, ginseng, and vitamins (especially vitamin E), have been determined to be nonmonograph conditions. Any drug product marketed for use as an OTC stimulant that is not in conformance with the monograph (21 CFR Part 340) may be considered a new drug within the meaning of section 310(p) of the Fedral Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352 and may not be marketed for this use unless it is the subject of an approved application.

The agency has examined the economic consequences of this final rule 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 final rule for OTC stimulant 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, the requirement for a Regulatory Flexibility Analysis under the Regulatory Flexibility Act does not apply to this final rule for OTC stimulant drug products because the proposed rule was issued prior to January 1, 1981, and is therefore exempt.

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.

List of Subjects in 21 CFR Part 340

Labeling, Over-the-counter drugs, Stimulant drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended by adding new Part 340, to read as follows:

PART 340—STIMULANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
340.1 Scope.
340.3 Definition.

Subpart B—Active Ingredient

340.10 Stimulant active ingredient.

Subpart C—Labeling

340.50 Labeling of stimulant drug products.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 335, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart A—General Provisions

§ 340.1 Scope.

(a) An over-the-counter stimulant drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part and each of the general conditions established in § 330.1.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 340.3 Definition.

As used in this part:

Stimulant. A drug which helps restore mental alertness or wakefulness during fatigue or drowsiness.

Subpart B—Active Ingredient

§ 340.10 Stimulant active ingredient.

The active ingredient of the product consists of caffeine when used within the dosage limits established in § 340.50(d).

Subpart C—Labeling

§ 340.50 Labeling of stimulant drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "alertness aid" or a "stimulant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "Helps restore mental alertness or wakefulness when experiencing fatigue or drowsiness." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of 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.

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

(1) "The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat."

(2) "For occasional use only. 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").

(3) "Do not give to children under 12 years of age."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": Adults and children 12 years of age and over: Oral dosage is 100 to 200 milligrams not more often than every 3 to 4 hours.

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Frank E. Young,

Commissioner of Food and Drugs.

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