mellorine to have the same fat content as ice cream.

The Commissioner disagrees. Under the imitation regulations, the Commissioner will not regard a product as nutritionally inferior solely because of a reduction in the fat content of a food. In addition, for technological reasons, the maximum level of vegetable fat that can be used in mellorine before there is an adverse effect on the physical attributes of the food is about 8 percent. In contrast to additional levels of milk fat, vegetable fat does not add to the flavor of the food. Mellorine will be named and labeled as a product distinctive from both ice cream (at a minimum of 10 percent milk fat) and ice milk (which ranges from 2 to 7 percent milk fat).

7. *Polysorbate 65 and polysorbate 80.* A manufacturer of polysorbate 65 and polysorbate 80 filed an objection and requested a hearing: The regulations governing the use of polysorbate 65 and polysorbate 80 under §§ 172.838 and 172.840 (21 CFR 172.838 and 172.840, formerly §§ 121.1008 and 121.1009, prior to recodification published in the FEDERAL REGISTER of March 15, 1977 (42 FR 14302)) now provide that they may be used alone or in combination for the manufacture of ice cream, frozen custard, ice milk, fruit sherbet, and nonstandardized frozen desserts. The establishment of a standard of identity for mellorine without revising §§ 172.838 and 172.840 would preclude the use of either of these ingredients in mellorine.

The Commissioner advises that §§ 172.838 and 172.840 are currently being revised to provide for the specific use of polysorbate 65 and polysorbate 80, respectively, in mellorine.

It has been brought to the Commissioner's attention that there was a typographical error in the July 25, 1974 final regulation for mellorine: In § 135.130(a)(2) the protein efficiency ratio for whole milk protein incorrectly listed as 120 percent of casein is changed to 108 percent of casein. In addition, a comment on the standard of identity for frozen desserts indicated confusion about the requirement, found both in that standard and this one, that the food have a specified PER as determined by a certain method of analysis.

The Commissioner advises that the regulation requires food to meet the specified PER value, but it does not independently require use of the official method of analysis. The regulations specified an official method of analysis solely to provide an authoritative means of resolving uncertainties and disputes in questionable cases. The manufacturer need not incur the expense of using the official method of determining the PER value so long as he correctly determines that the food satisfies the PER value specified in the regulation as determined by the official method.

The final regulation for other frozen desserts published elsewhere in this issue of the FEDERAL REGISTER contains, under § 135.3, a definition for pasteurized mix applicable to the subject standard for mellorine. Therefore, paragraph (c) of § 135.130 is deleted and paragraphs (d), (e), and (f) are redesignated paragraphs (c), (d), and (e).

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 401, 701(e), 52 Stat. 1046 as amended, 70 Stat. 919 as amended (21 U.S.C. 341, 371(e))) and under authority delegated to the Commissioner (21 CFR 5.1), notice is given that no objections raising substantial issues of fact requiring a hearing under section 701(e) of the act were received. Accordingly, the requests for a hearing on the objections are denied. Further, in accordance with the foregoing: *It is ordered,* That § 135.130 as promulgated in the FEDERAL REGISTER of July 25, 1974 (39 FR 27128) be revised to read as follows:

§ 135.130 Mellorine: identity; label statement of optional ingredients.

(a) *Description.* (1) Mellorine is a food produced by freezing, while stirring, a pasteurized mix consisting of safe and suitable ingredients including, but not limited to, milk-derived nonfat solids and animal or vegetable fat, or both, only part of which may be milkfat. Mellorine is sweetened with nutritive carbohydrate sweetener and is characterized by the addition of flavoring ingredients.

(2) Mellorine contains not less than 1.6 pounds of total solids to the gallon, and weighs not less than 4.5 pounds to the gallon. Mellorine contains not less than 6 percent fat and 2.7 percent protein having a protein efficiency ratio (PER) not less than that of whole milk protein (108 percent of casein) by weight of the food, exclusive of the weight of any bulky flavoring ingredients used. In no case shall the fat content of the finished food be less than 4.8 percent or the protein content be less than 2.2 percent. The protein to meet the minimum protein requirements shall be provided by milk solids, not fat and/or other milk-derived ingredients.

(3) When calculating the minimum amount of milkfat and protein required in the finished food, the solids of chocolate or cocoa used shall be considered a bulky flavoring ingredient. In order to make allowance for additional sweetening ingredients needed when certain bulky ingredients are used, the weight of chocolate or cocoa solids used may be multiplied by 2.5; the weight of fruit or nuts used may be multiplied by 1.4; and the weight of partially or wholly dried fruits or fruit juices may be multiplied by appropriate factors to obtain the original weights before drying and this weight may be multiplied by 1.4.

(b) *Fortification.* Vitamin A is present in a quantity which will ensure that 40 international units (IU) are available for each gram of fat in mellorine, within limits of good manufacturing practice.

(c) *Methods of analysis.* Fat and protein content, and the PER shall be determined by the following methods contained in the "Official Methods of Analysis of the Association of Official Analytical Chemists," 12th ed., 1975.[1]

(1) Fat content shall be determined by the method: "Fat, Roese-Gottlieb Method—Official Final Action," section 16.228.

(2) Protein content shall be determined by one of the following methods: "Nitrogen—Official Final Action," Kjeldahl Method, section 16.226, or Dye Binding Method, section 16.227.

(3) PER shall be determined by the method: "Biological Evaluation of Protein Quality-Official Final Action" sections 39.166–39.170.

(d) *Nomenclature.* The name of the food is "mellorine." The name of the food on the label shall be accompanied by a declaration indicating the presence of characterizing flavoring in the same manner as is specified in § 135.110(c).

(e) *Label declaration.* The common or usual name of each of the ingredients used shall be declared on the label as required by the applicable sections of Part 101 of this chapter, except that sources of milkfat or milk solids not fat may be declared, in descending order of predominance, either by the use of the terms "milkfat, and nonfat milk when one or any combination of two or more ingredients listed in § 101.4(b) (3), (4), (8), and (9) of this chapter are used, or alternatively as permitted in §101.4 of this chapter.

Effective date: Compliance with the regulation, including any labeling changes required, may have begun on September 23, 1974, and all products initially introduced into interstate commerce on or after July 1, 1979 shall fully comply.

(Secs. 401, 701(e), 52 Stat. 1046 as amended, 70 Stat. 919 as amended (21 U.S.C. 341, 371(e)).)

Dated: April 4, 1977.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.77-10625 Filed 4-11-77;8:45 am]

SUBCHAPTER D—DRUGS FOR HUMAN USE

[Docket No. 75N-0039]

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

Subpart B—Administrative Procedures

TESTING OF CATEGORY III ACTIVE INGREDIENTS

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This regulation establishes the conditions under which an over-the-counter (OTC) drug classified in Cate-

[1] Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Ben Franklin Station, Washington, D.C. 20044.

gory III (insufficient data to permit final classification at this time) may continue to be marketed pending development of data to support approval of the ingredient, labeling, or other condition as safe, effective, and not misbranded, through amendment of the applicable OTC drug monograph or approval of a new drug application (NDA). This order is based on a proposal issued in response to numerous requests for clarification of such conditions.

EFFECTIVE DATE: June 13, 1977.

FOR FURTHER INFORMATION CONTACT:

William D. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs proposed, in a notice published in the FEDERAL REGISTER of October 21, 1975 (40 FR 49097), to amend § 330.10 (21 CFR 330.10), the procedural regulations governing the OTC drug review project. Interested persons were invited to comment on the proposal by December 22, 1975.

In response to the proposal, comments were received from one trade association, six drug manufacturers, one consumer group, one citizen, and one pharmacy school. The comments on this proposal and the Commissioner's conclusions concerning them are as follows:

1. Several comments argued that permitting products with Category III conditions to remain on the market pending further testing is beyond the authority of the Food and Drug Administration (FDA). The comments contended that products that require further testing cannot be regarded as generally recognized as safe and effective, and so must be new drugs whose marketing cannot be allowed unless approval of an NDA has been obtained.

The establishment of Category III and the issues related to the status and treatment of products with conditions in that category have been discussed before. The Commissioner responded fully to comments suggesting deletion of Category III in connection with the proposed and final orders regarding procedures for classification of OTC drugs published in the FEDERAL REGISTER of January 5, 1972 (37 FR 85) and May 11, 1972 (37 FR 9464).

As stated in paragraph 72 at page 9470 of the May 11, 1972 regulation, the OTC drug review is intended to identify not only those drugs that are generally recognized as safe and effective, but also those that are not generally recognized as safe and effective, and those that require further testing before a determination of general recognition of safety and effectiveness may be made.

One of the comments cited the Supreme Court's holding in *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973), as supporting the proposition that permitting the marketing of drugs in Category III is contrary to the Federal Food, Drug, and Cosmetic Act (hereafter "the act"). However, the comment failed to cite *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973), a companion case handed down the same day. That case recognized the agency's primary jurisdiction "for determining whether particular OTC products, not covered by NDA's are safe products, not ineffective, and not misbranded," and specifically endorsed the OTC drug review as an appropriate administrative process (412 U.S. at 650). The Court then noted that the types of complex chemical and pharmacological determinations required for an extensive review of the safety and effectiveness of ingredients and combinations of ingredients should be left to the agency that has the requisite expertise (412 U.S. 653–654). Although the Court did not expressly address the status of drugs not found to be generally recognized as safe and effective on the basis of existing data, it is implicit in its decision that the primary jurisdiction of FDA includes the discretion to distinguish between drugs that are not generally recognized as safe and effective (Category II) and those that may be generally recognized as safe and effective if additional testing is conducted (Category III), and to permit continued marketing of products in the latter category pending the results of necessary investigations.

The Commissioner also notes that, contrary to the assertion of the same comment, Judge Bryant's order filed on October 11, 1972 pursuant to his decision in *American Public Health Association* v. *Veneman*, 349 F. Supp. 1311, 1315 (D.D.C. 1972), explicitly recognized that OTC drugs could be reviewed and handled pursuant to the procedure established in the May 11, 1972 regulation. The court acknowledged the OTC drug review process and specifically exempted drugs in the OTC drug review from its order requiring the agency to take action on National Academy of Sciences/National Research Council (NAS/NRC) drug reports. Category III has been an integral part of the OTC drug review from the outset, and it is unrealistic to assume that the court was not aware of the purpose and effect of Category III when it issued its order.

The Commissioner concludes that Category III classification of ingredients, claims, or combinations does not automatically confer "new drug" status, as suggested in these comments. This review is a massive consolidation and upgrading of knowledge concerning hundreds of thousands of OTC products, some of which have been sold in the United States for more than 100 years. The statute cannot reasonably be interpreted as mandating the impractical result of classifying every ingredient, claim, or combination associated with these products as "new" or "old" with no time permitted to refine the data base on which such a decision must be made. It is well within the agency's rule making authority to establish an orderly administrative process by which older products that may have been marketed for years without evaluation can continue to be marketed while they are evaluated in terms of modern scientific and technical methodology to determine whether or not they are in fact generally recognized by experts as safe and effective under their intended conditions of use.

The Commissioner emphasizes that if a serious safety question respecting an ingredient is identified, the agency will take action to remove the ingredient from the marketplace. This may occur following the orderly OTC drug review process or, if serious safety questions arise, on a much more expedited basis such as occurred with the recommendation of the OTC antimicrobial panel to remove both hexachlorophene and tribromsalan from the OTC marketplace before publication of a final monograph.

2. One comment urged that testing should begin immediately after an ingredient, claim, or combination is classified in Category III.

It is unclear whether the comment would have testing begin as soon as an advisory panel report and proposed monograph are issued or at a later date, e.g., when a final OTC drug monograph is promulgated.

A requirement that Category III testing begin on the date of publication of the panel report and proposed monograph would bypass agency review of an advisory panel's recommendations, thus compromising the due process principles upon which the OTC drug review is founded.

The Commissioner concludes that Category III testing should not be required until after completion of the established OTC administrative procedures, i.e., agency review of the advisory panel report, recommendation, and proposed monograph; the tentative final monograph; and the final monograph. Opportunity for public review and comment is provided at each stage, and the content of Category III is thus not fixed until publication of the final monograph.

Requiring that testing begin for Category III conditions immediately upon publication of a final monograph could in many cases be wasteful and disruptive. A reasonable time should be provided in which firms can elect between testing an ingredient or claim in Category III or removing the Category III condition by reformulation and/or relabeling in compliance with the final monograph.

The Commissioner concludes that, although testing should commence expeditiously after publication of the final monograph, a requirement that testing begin immediately is unnecessary and unsound.

The Commissioner notes that testing of Category III claims by manufacturers has often voluntarily preceded issuance of final OTC drug monographs and has frequently been undertaken during the period of panel deliberations. The Commissioner is encouraged by such voluntary actions on the part of drug manufacturers.

3. One comment asked if the Commissioner should not merely invoke the provisions of section 503(b) of the act (21 U.S.C. 353(b)) when a drug has been found, at the conclusion of Category III testing, to be generally recognized as safe and effective for prescription use but not for OTC use. The comment also stated that the proposed regulation did not distinguish between drugs placed in Category III because of insufficient evidence of safety for OTC use and those placed in Category III because of insufficient evidence to establish that they are generally recognized as safe and effective.

The Commissioner advises that classification of an ingredient in Category III represents a determination that an ingredient is capable of being shown to be generally recognized as safe and effective under the specific condition of OTC use. The data yielded by Category III testing may demonstrate that the ingredient is generally so recognized, and, if it does, the ingredient will be classified in Category I upon submission and approval of a proposed amendment to the monograph.

The data may indicate, however, that the ingredient does not meet the criteria for general recognition of safety and effectiveness, but that products containing the ingredient may appropriately be marketed as new drugs for OTC use. Such would be the case when the data, while demonstrating the safety and effectiveness of an ingredient do not establish that such safety and effectiveness have achieved general recognition, but also do not establish that the ingredient poses the kind or degree of risk that requires limitation to prescription sale.

If the data from Category III testing, or from reports of actual experience with drugs, reveal the kind or degree of risk that requires products containing the ingredient to be limited to prescription sale, then the ingredient cannot be regarded as generally recognized as safe and effective for OTC use. In such a case, the Commissioner may invoke the provisions of section 503(b) of the act to limit the drug to prescription use. If the data also establish that the ingredient cannot be regarded as generally recognized as safe and effective for prescription use, the Commissioner may require that drugs containing the ingredient be subject to regulation as new drugs as well.

The Commissioner emphasizes that, although panels may appropriately consider questions of safety of ingredients for OTC as opposed to prescription availability, and comment may be requested on those questions in OTC rule making proceedings, the primary purpose of the OTC drug review is to determine which ingredients are generally recognized as safe and effective for OTC use. An ingredient that cannot be so classified must be dealt with pursuant to other regulatory mechanisms as the Commissioner deems appropriate in any particular case. Although the results of Category III testing of an ingredient that cannot be classified in Category I would be relevant to the manner in which the Commissioner exercises his authority, it does not follow that these results would permit the status of every such ingredient to be readily resolved as a byproduct of the OTC drug review.

4. One comment requested clarification of what is meant by "old drug monograph."

A more precise term is "OTC drug monograph," which will be used hereafter in the context of the OTC drug review. An OTC drug monograph is a drug class standard under which products can be marketed without preclearance by the agency and still meet the requirements for safety, effectiveness, and adequate directions for use as required by the act. Thus, an OTC drug monograph provides for assuring the safety and effectiveness of OTC drugs by means other than the extensive and exhaustive product-by-product review, as in the preclearance procedures of the NDA process.

5. Several comments evidenced confusion about the procedure for obtaining Category I classification of a Category III condition.

The Commissioner advises that the procedure involves submission of a petition to the agency for a proposal to amend the applicable OTC drug monograph to include the condition in question. The petition should be in the form of a citizen petition, as described in § 10.30 (21 CFR 10.30) (formerly § 2.7, prior to recodification published in the FEDERAL REGISTER of March 22, 1977 (42 FR 15553)) of the FDA Administrative Practices and Procedures published in the FEDERAL REGISTER of January 25, 1977 (42 FR 4680). The statement of grounds should include, or refer to, all Category III testing data, including negative findings. The Commissioner will evaluate the petition and determine whether to grant or deny it. If he denies it, the petitioner may seek review of the denial in a proper court. If he grants the petition, the Commissioner will publish in the FEDERAL REGISTER a proposal to amend the applicable OTC drug monograph. Thereafter, he will allow an opportunity for public comment on the proposed amendment for 60 days, followed by publication of a final amendment. In lieu of, or in addition to, submitting a petition to amend an OTC drug monograph to include the Category III condition, a manufacturer may submit an NDA.

The Commissioner notes that the procedures in § 330.10(a)(12) for a petition to amend an OTC drug monograph were first proposed to be modified in the FDA proposed Administrative Practices and Procedures published in the FEDERAL REGISTER of September 3, 1975 (40 FR 40682). No comments were received on either proposal, and this final regulation incorporates both the September 1975 and the October 1975 proposals. This change, applicable only to monograph amendments, provided for deletion of the tentative final monograph and oral hearing stages of the present OTC procedures which were thought to be unnecessarily burdensome to effect a change in an already established monograph. Thus, OTC monographs would be amended in the same manner as other regulations, i.e., through publication of a proposal, time for comment, followed by publication of the final order. The Commissioner has further revised § 330.10(a)(12) to clarify this administrative process.

6. Several comments regarding proposed § 330.10(a)(12)(ii) stated that it would be duplicative, wasteful, and burdensome to small manufacturers to require that each manufacturer undertake testing or have it undertaken on his behalf as a condition for the continued marketing of his products with Category III conditions during the testing period specified in the monograph.

The Commissioner agrees with these comments and is modifying the testing requirements, which have now been moved to new § 330.10(a)(13), to provide that all manufacturers' products with Category III conditions may continue to be marketed during the period specified in the final report for Category III testing provided the number of studies specified in the applicable testing guidelines are undertaken to demonstrate that such conditions are generally recognized as safe and effective and not misbranded, as the case may be, even though such studies are not conducted by every manufacturer.

The Commissioner concludes that to require each firm to undertake testing would not be in the public interest because it would result in repetitive and unnecessary human experimentation and because it would be wasteful, not only of the money spent for the tests, but also of the time spent by the limited number of clinical investigators available to perform such tests. He further concludes that the testing required in the proposal would be duplicative, wasteful, and burdensome not only to small manufacturers but also to large ones, especially those firms that have numerous products with a Category III ingredient or claim.

Classification of an ingredient or claim in Category III represents a preliminary determination that general recognition of safety and effectiveness can be shown with further testing. Whether such general recognition exists depends on the demonstration of scientific facts by reliable studies. What is important, therefore, is that the required number of studies be performed, not that they be duplicated by each manufacturer that markets a product with a Category III condition. This has been the approach consistently taken with respect to classification of products in Category I; i.e., if sufficient data exist to justify a finding that an ingredient or claim is generally recognized as safe and effective and not misbranded (Category I), all products containing that ingredient or making that claim are regarded as generally so recognized even though the data were not developed specifically in relation to, or by manufacturers of, those products. Accordingly, if data from reliable studies, or from one study if only one study is required in the testing guidelines, demonstrate that an ingredient or claim is generally recognized as safe

and effective and not misbranded, the agency may properly grant a petition to amend the applicable OTC drug monograph regardless of whether such data were generated by one manufacturer, by more than one, or by all. The extent of additional testing required to reclassify an ingredient from Category III to Category I (i.e., one study or more than one study) will be specified in the applicable testing guidelines.

Since each firm is not required to undertake a study, the Commissioner encourages firms to cooperate and work with each other in arranging for the necessary study or studies. If more than one study is required, it is not necessary that they be sponsored by the same person, firm, or other organization.

In addition, the Commissioner urges that trade associations work with firms to see that the necessary study or studies are conducted. In fact, a study may be sponsored by a trade association. It is only as a result of such cooperation that unnecessary and repetitive human testing will be avoided.

7. Several comments suggested that a mechanism be provided for ensuring that each manufacturer of a product with a Category III condition does in fact undertake meaningful testing. The proposed regulation required that manufacturers furnish proof of such testing to FDA upon request. The comments contended that this approach is not adequate and suggested that the agency require submission of protocols and periodic progress reports.

The Commissioner agrees that a suitable mechanism must exist for the agency to determine that Category III testing is being performed. However, for the agency, which has limited resources and tight budget constraints, to require the submission of protocols and periodic progress reports for each ingredient and claim to be tested would seriously hinder its ability to discharge other commitments important to the public health. The Commissioner has concluded that a more practical approach is to require notification that the appropriate testing for each Category III ingredient or claim is planned, and subsequent notification that it has, in fact, been initiated.

Each person, group of persons, or trade association that plans to sponsor a study shall submit a Category III notification statement in quintuplicate to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857. This notification shall be submitted within 60 days after the date of publication of the final monograph. Each statement shall contain: (a) name and address of sponsoring agent (manufacturer, distributor, supplier, trade association, etc.) responsible for assuring that testing is undertaken, (b) name and address of each person directly responsible for monitoring the studies, (c) each Category III condition being tested in the manner suggested in the applicable final regulation for that class of drugs, and (d) the anticipated date that testing will be initiated, which shall be prior to the date after which a product with a Category II condition may no longer be shipped in interstate commerce. Upon written request or notice in the FEDERAL REGISTER, the sponsoring agent shall furnish to the Food and Drug Administration evidence of the type of testing being performed, e.g., in vitro, animal, human, survey or other, and/or other information and data appropriate to the testing being conducted.

As soon as possible after the date that the Category III notification statements are due, a notice will be published in the FEDERAL REGISTER indicating (1) each Category III ingredient or claim for which notification has been received that the number of studies specified in the applicable testing guidelines are being conducted, and (2) each Category III ingredient or claim for which no notification has been received that the required number of studies are being conducted. The notice will place in Category II those claims or ingredients for which no notification that the required number of studies are being conducted has been received, and indicate the date when products containing such ingredients or claims may no longer be shipped in interstate commerce. Products containing ingredients or claims for which studies are being performed may be marketed by anyone, including a new manufacturer during the testing period.

In addition to submitting the Category III notification statement, each sponsor of a study will be required to submit a supplement to the notice indicating the date testing was begun. This supplement must be submitted within 10 days of the initiation of the testing and must also be submitted prior to the date after which a product with a Category II condition may no longer be shipped in interstate commerce. If within that time period the agency does not receive notification that studies have been initiated, the result will be reclassification of the ingredient or claim from Category III to Category II.

Instead of placing the requirements for testing Category III conditions under the hearing "Amendment of monographs," as in the proposal, the Commissioner has placed these requirements in new § 330.10(a)(13), with the heading "Testing of Category III conditions." This new paragraph embraces the requirements discussed in the replies to comments 6 and 7. The Commissioner is also reversing the order of the provisions in proposed paragraph (a)(12) relating to submission of petitions to amend an OTC drug monograph and submission of a new drug application.

8. A comment suggested that additional manufacturers, other than those with affected products already on the market, may desire to initiate marketing of products with Category III ingredients, claims, or combinations while the required testing is conducted.

The Commissioner finds that it would be unreasonable and unenforceable to bar initial marketing of such products where other products with the same Category III ingredients, claims, or combinations are presently on the market. Therefore, as indicated previously, new manufacturers may introduce products containing a Category III ingredient or claim as long as the agency has been notified that studies are being conducted to reclassify such ingredient or claim in Category I. The new manufacturer would not have to conduct any testing to upgrade the Category III claim or ingredient in order to market the product.

9. One comment noted that the proposed regulation specifies that Category III testing must be initiated, either by the marketer or on his behalf, prior to the date after which a product with an ingredient, claim, or combination subject to Category II may no longer be shipped in interstate commerce. It was urged that the agency be flexible in applying the cutoff date for initiation of Category III testing.

The Commissioner has concluded that because of the need for uniform labeling in the marketplace, the desirability of expediting the transition of relabeled and reformulated products, and because adequate time has been provided for the transition, the effective dates specified in OTC drug monographs will be rigidly enforced.

10. In another comment, it was noted that provision has been made for FDA to handle an NDA as a petition for amendment of a monograph under certain conditions, but that there is no provision for a firm to convert a petition to amend a monograph to an NDA. Implicit in this comment is the understanding that documents submitted either as petitions to amend a monograph or as NDA's may be recharacterized by the agency and that such a recharacterization yields entirely different administrative results: the petition process is completely open and public and is intended to produce a monograph amendment under which an ingredient, claim, or combination is considered generally recognized as safe and effective, and therefore may be marketed by anyone; the NDA process, however, is largely confidential and results in private licensure for manufacture of products subject to approved NDA's.

The Commissioner concludes that, if a manufacturer wishes his petition for amendment of a monograph to be reconsidered as an NDA, he may convert his petition to an NDA as if it had never been filed as a petition. However, during the Category III testing period, the manufacturer may not market his product with any ingredient, claim, or combination that is the subject of the NDA until after approval of the NDA is obtained.

The Commissioner wishes to make clear that he will view with some reservation attempts to submit an NDA for a product with a Category III ingredient, claim, or combination. Classification of an ingredient, claim, or combination in Category III represents a preliminary determination that it is capable, with further testing, of being regarded as generally recognized as safe and effective and may then be marketed by any person, subject to the terms of the applicable monograph (as amended). An NDA is a private license. It may properly be sought

only for an ingredient, claim, or combination that is not, and, even with additional testing, is unlikely to be, generally recognized as safe and effective. It will therefore be inappropriate in most cases for a product with a Category III condition to be the subject of an NDA for the condition so classified. If the Commissioner concludes that the ingredient, claim, or combination in question is not generally recognized as safe and effective, and is unlikely to achieve such status on the basis of further testing, he will not classify it in Category III, but in Category II.

Consistent with the basis for Category III classification (that general recognition of safety and effectiveness can be shown) and with the purpose of Category III testing (to establish the existence of such general recognition with a view to petitioning the Commissioner to amend the applicable OTC drug monograph), the Commissioner concludes that all data and information accompanying a petition to amend a monograph to include a Category III condition will be publicly available upon receipt of the petition. Unlike safety and effectiveness for a product for which an NDA is sought, general recognition of safety and effectiveness for a Category III product subject to a petition to amend must be based on data and information that are in the public domain and therefore available to the community of experts, without restriction. Confidentiality of data relating to safety and effectiveness is incompatible with Category III status, which looks toward establishment of general recognition of such safety and effectiveness. The Commissioner believes that, as a practical matter, little, if any, "proprietary" information will be generated in the course of carrying out Category III testing guidelines, which will usually be quite specific. Whether such information is generated or not, however, the Commissioner concludes that general recognition of safety and effectiveness cannot, as a definitional matter, be shown by reference to confidential material (see *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 632 (1973); *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973)) and, therefore, that all data and information submitted with a petition to amend a monograph to include a condition previously classified in Category III will become publicly available when the petition is received.

11. A comment suggested that the criteria governing the choice between submission of an NDA or a petition would appear to be improper. Under the proposal, a manufacturer may submit an NDA in lieu of a petition if he has not marketed the ingredient, claim, or combination during the interim marketing period for products with Category III conditions; if he has conducted all clinical testing pursuant to an NDA plan; and if he has undertaken no marketing prior to approval of the NDA. The comment stated that the correct standard for determining when data should be submitted as part of an NDA rather than in a petition to amend a monograph is, instead, whether the data establish only actual safety and effectiveness rather than general recognition of safety and effectiveness.

The Commissioner concludes that the submitting firm may appropriately make the initial decision whether to petition to amend the monograph or, instead, submit an NDA. The firm's decision is not binding on the Commissioner, who will determine whether the submission establishes general recognition and, therefore, should be in the form a petition to amend the monograph, or whether general recognition is not established by the submission, in which case the submission should be in the form of an NDA. Should testing indicate that general recognition cannot be established as originally thought, the Commissioner believes it fair and reasonable to allow a submitting firm to change its submission from a petition to an NDA. Therefore, no change has been made in the criteria governing the choice between submission of an NDA or a petition.

12. There was comment that the requirement for submitting petitions to amend a monograph prior to 60 days before the end of the period for Category III testing would unduly shorten the time period allowed for testing.

The Commissioner believes that the OTC drug review procedures provide ample time for Category III testing. Also, it is not necessary to wait for issuance of the final monograph to start such testing. The intent and design of the review process is to encourage changes in formulations and labeling, and initiation of testing, on a current and continuing basis. The Commissioner has determined that agency testing guidelines will most likely be finalized at the tentative final monograph stage to assist manufacturers who wish to voluntarily begin testing to do so as soon as possible.

The Commissioner concludes that requiring submission of amendment petitions and supporting data prior to 60 days before the expiration date of the period permitted for testing of Category III conditions is reasonable. The time is needed to permit the agency preliminarily to review the information submitted and reject patently deficient data If it appears that more time should be allowed than is provided for Category III testing in a particular advisory panel report, this should be suggested in comments to the proposed and tentative final monograph. In addition, the agency will consider requests for extensions of time. Such a request should generally not be submitted until approximately 6 months prior to the expiration date of the testing period provided; earlier requests would necessarily be based on speculation about how expeditiously the testing can be accomplished.

The Commissioner notes that the terms Category I, Category II, and Category III are used throughout this document. To fully clarify the meaning of these terms, the Commissioner has decided to amend the appropriate paragraphs of § 330.10 to refer to these terms expressly.

Therefore, under the Federal Food, Drug, and Cosmetic Act (Secs. 201, 502, 505, 701(a), 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055 (21 U.S.C. 321, 352, 355, 371(a))) and under the authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), § 330.10 is amended by revising paragraphs (a)(5)(i), (ii), and (iii) and (6)(i), (ii), and (iii), and (12); and by adding new paragraph (a)(13) to read as follows:

§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and as not misbranded, and for establishing monographs.

* * * * *

(a) * * *

(5) * * *

(i) A recommended monograph or monographs covering the category of OTC drugs and establishing conditions under which the drugs involved are generally recognized as safe and effective and not misbranded (Category I). This monograph may include any conditions relating to active ingredients, labeling indications, warnings and adequate directions for use, prescription or OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph.

(ii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding (Category II).

(iii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that the available data are insufficient to classify such condition under either paragraph (a)(5)(i) or (ii) of this section and for which further testing is therefore required (Category III). The report may recommend the type of further testing required and the time period within which it might reasonably be concluded.

(6) * * *

(i) A monograph or monographs establishing conditions under which a category of OTC drugs is generally recognized as safe and effective, and not misbranded (Category I).

(ii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding (Category II).

(iii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that the available data are insufficient to classify such conditions under either paragraph (a)(6)(i) or (ii) of this section (Category III).

* * * * *

(12) *Amendment of monographs.* The Commissioner may propose on his own initiative to amend or repeal any monograph established pursuant to this section. Any interested person may petition the Commissioner for such proposal pursuant to § 10.30 of this chapter. The Commissioner may deny the petition if he finds a lack of safety or effectiveness employing the standards in paragraph (a) (4) of this section (in which case the appeal provisions of paragraph (a) (11) of this section shall apply), or he may publish a proposed amendment or repeal in the FEDERAL REGISTER if he finds general recognition of safety and effectiveness employing the standards in paragraph (a) (4) of this section. Any interested person may, within 60 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk, Food and Drug Administration, written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed in the office of the Hearing Clerk between the hours of 9 a.m. and 4 p.m., Monday through Friday. After reviewing the comments, the Commissioner shall publish a final order amending the monograph established under the provisions of paragraph (a) (9) of this section or withdraw the proposal if comments opposing the amendment are persuasive. A new drug application may be submitted in lieu of, or in addition to, a petition under this paragraph.

(i) A petition to amend the applicable OTC drug monograph to include a condition subject to paragraph (a) (6) (iii) (Category III) of this section shall be submitted prior to 60 days before the expiration date for such condition. The petition shall include all Category III testing data, including negative findings, relating to the condition that is the subject of the amendment. If a petition is received that includes data from studies undertaken pursuant to paragraph (a) (13) of this section, marketing of all drug products with that condition may thereafter continue unless and until the petition is disapproved or until the Commissioner, as a result of the procedures in this paragraph, determines that the condition should be classified in Category II. The Food and Drug Administration shall handle a petition for amendment of an OTC drug monograph as a new drug application, and shall review it on that basis, if the provisions of this paragraph preclude granting such a petition but permit approval of a new drug application. However, until the agency determines whether or not an approved new drug application can issue, the data submitted will be considered as a petition for amendment of an OTC drug monograph, and marketing may be continued.

(ii) A new drug application may be submitted in lieu of a petition to amend the OTC drug monograph only if the drug product with the condition that is the subject of the new drug application has not been marketed on an interim basis (such as under the provisions of paragraph (a) (6) (iii) (Category III) of this section), all clinical testing has been conducted pursuant to a new drug application plan, and no marketing of the product with the condition for which approval is sought is undertaken prior to approval of the new drug application. The Food and Drug Administration shall handle a new drug application as a petition for amendment of a monograph, and shall review it on that basis, if the provisions of this paragraph preclude approval of a new drug application but permit the granting of such a petition.

(13) *Testing of Category III conditions.* (i) After publication of the final monograph, any product with a condition (e.g., ingredient, labeling claim, combination of ingredients) subject to paragraph (a) (6) (iii) (Category III) of this section may remain on the market, or may be introduced into the market, provided that the Food and Drug Administration receives notification that the number of studies specified in the applicable testing guidelines will be undertaken to obtain the data necessary to resolve the issues that resulted in such classification.

(ii) Such notification shall be submitted to the Food and Drug Administration by each sponsor of a study within 60 days after the date of publication of the final monograph. A sponsor may be a person, a firm, a group of firms, or a trade association.

(iii) Such notification shall be in the form of a Category III Notification Statement and shall be submitted in quintuplicate to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857. A Category III Notification Statement shall contain: (*a*) name and address of the sponsor of the study, (*b*) name and address of each person directly responsible for monitoring the study, (*c*) each Category III condition being tested in the manner suggested in the applicable final regulation for that class of drugs, and (*d*) the anticipated date that testing will be initiated, which shall be prior to the date after which a product with a condition subject to paragraph (a) (6) (ii) (Category II) of this section may no longer be shipped in interstate commerce.

(iv) A copy of each Category III Notification Statement shall be maintained in a permanent file for public review in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, Md. 20857. Upon written request or notice in the FEDERAL REGISTER, the manufacturer or distributor shall furnish to the Food and Drug Administration evidence of the type of test being performed (e.g., in vitro, animal, human, survey, or other), and/or other information and data appropriate to the testing being conducted.

(v) As soon as possible after the date for submitting a Category III Notification Statement, the Food and Drug Administration will issue in the FEDERAL REGISTER a notice listing each Category III condition for which notification statements have been filed stating that the required studies will be undertaken. Such notice shall also list each Category III condition for which the required number of notification statements have not been received and shall place these conditions in Category II, indicating the date when products containing such conditions may no longer be shipped in interstate commerce.

(vi) Within 10 days of initiating the study, which shall be prior to the date after which a product with a condition subject to paragraph (a) (6) (ii) (Category II) of this section may no longer be shipped in interstate commerce, each sponsor shall submit a supplement to his notification statement indicating the exact date testing was initiated. Such supplement shall be submitted in quintuplicate to the same address as the notification statement. The failure of the agency to receive within such time period notification that the required studies have been initiated shall result forthwith in publication of a notice in the FEDERAL REGISTER reclassifying the condition from Category III to Category II.

(vii) A sponsor of a study is responsible for advising the Food and Drug Administration of the termination of such study. If the Commissioner determines, on the basis of his own inquiries or from advice received from sponsors of studies, that the required studies are no longer being carried out, he shall forthwith issue in the FEDERAL REGISTER a notice reclassifying the condition from Category III to Category II.

Effective date. This regulation shall be effective on June 13, 1977.

(Secs. 201, 502, 505, 701(a), 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055 (21 U.S.C. 351, 352, 355, 371(a)).)

Dated: April 2, 1977.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc.77–10601 Filed 4–11–77;8:45 am]

[Docket No. 77N–0032]

PART 430—ANTIBIOTIC DRUGS—GENERAL

PART 601—LICENSING

Recodification Editorial Amendments; Correction

AGENCY: Food and Drug Administration, HEW.

ACTION: Correction.

SUMMARY: This document corrects a final rule that appeared at page 15673 in the FEDERAL REGISTER of Tuesday, March 22, 1977 (FR Doc. 77–7952).

EFFECTIVE DATE: April 12, 1977.

FOR FURTHER INFORMATION CONTACT:

John Richards, 202–443–2994.

The following corrections are made:

1. On page 15675, left column, § 430.20 is corrected in paragraph (b) (2) by changing "12.5(c)" to read "12.20(c)."

2. On page 15676, left column, § 601.4 (b) is corrected by changing "§ 12.20(b)" to read "§ 12.21(b)."