Proposed Rules

Federal Register
Vol. 64, No. 243
Monday, December 20, 1999

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 330

[Docket No. 96N–0277]
RIN 0910–AA01

Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing additional criteria and procedures by which over-the-counter (OTC) conditions may become eligible for consideration in the OTC drug monograph system. The proposed criteria and procedures address how OTC drugs initially marketed in the United States after the OTC drug review began in 1972 and OTC drugs without any U.S. marketing experience could meet the statutory definition of marketing ''to a material extent'' and ''for a material time'' and become eligible. If found eligible, the condition would be evaluated for general recognition of safety and effectiveness in accordance with FDA's OTC drug monograph regulations. FDA is also proposing changes to the current OTC drug monograph procedures to streamline the process and provide additional information in the review.

DATES: Submit written comments by March 22, 2000. See section V of this document for the effective date of any final rule that may issue based on this proposal.

ADDRESSES: Submit written comments on the proposed rule to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Wendy Taylor, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Donald Dobbs, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION:

I. Background

The OTC drug monograph system was established to evaluate the safety and effectiveness of all OTC drug products marketed in the United States before May 11, 1972, that were not covered by new drug applications (NDA's) and all OTC drug products covered by ''safety'' NDA's that were marketed in the United States before enactment of the 1962 drug amendments to the Federal Food, Drug, and Cosmetic Act (the act). In 1972, FDA began its OTC drug review to evaluate OTC drugs by categories or classes (e.g., antacids, skin protectants), rather than on a product-by-product basis, and to develop ''conditions'' under which classes of OTC drugs are generally recognized as safe and effective (GRAS/E) and not misbranded.

FDA publishes these conditions in the **Federal Register** in the form of OTC drug monographs, which consist primarily of active ingredients, labeling, and other general requirements. Final monographs for OTC drugs that are GRAS/E and not misbranded are codified in part 330 (21 CFR part 330). Manufacturers desiring to market an OTC drug covered by an OTC drug monograph need not seek FDA clearance before marketing.

In the **Federal Register** of October 3, 1996 (61 FR 51625), FDA published an advance notice of proposed rulemaking (ANPRM) stating that it was considering proposing to amend its regulations to include criteria under which certain additional OTC drug conditions may become eligible for inclusion in the OTC drug monograph system. Interested persons were invited to submit written comments by January 2, 1997. The agency received 16 comments, which it discusses in section III. of this document.

Under this proposal, eligibility for consideration in the OTC drug monograph system would be determined by showing a condition's use ''to a material extent'' and ''for a material time'' in compliance with the existing statutory requirements of the act. A number of ingredients have been marketed in OTC drug products under NDA's approved after May 11, 1972. The agency is providing criteria and procedures in this proposal for manufacturers who wish to have ingredients such as these considered for OTC drug monograph status.

For OTC drug products without any U.S. marketing experience, this proposal represents a change in the agency's previous interpretation of ''use'' requirements in section 201(p) of the act (21 U.S.C. 321(p)). Previously, the agency interpreted the use provision to mean use in the United States only. The agency is proposing this change in policy to expand use to include foreign marketing experience because it believes that under certain circumstances use outside the United States may appropriately be considered to satisfy the use requirements in section 201(p) of the act.

In the ANPRM, the agency used the term ''condition'' to refer to OTC drug active ingredients, indications, dosage forms, dosage strengths, routes of administration, and active ingredient combinations. In this proposal, the agency is clarifying that the term ''condition'' refers to an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration, marketed for a specific OTC use. The agency is adding the reference to botanical drug substance to clarify that the agency recognizes that the information needed for consideration of a botanical substance for inclusion in the OTC drug monograph system may differ from the information needed to evaluate other types of active ingredients for this purpose.

II. Description of the Proposed Rule

Currently, the OTC drug regulations in part 330 do not define eligibility requirements for consideration in the OTC drug monograph system or what constitutes marketing to a material extent or for a material time. This proposed rule sets forth criteria for defining material extent and material

time and procedures for considering additional ''conditions'' (as clarified in section I. of this document) in the OTC drug monograph system. The definition of ''conditions'' is included in proposed § 330.14(a).

Proposed § 330.14(b) describes the criteria for consideration for inclusion in the OTC drug monograph system. Proposed § 330.14(b)(1) would require that the condition be marketed for OTC purchase by consumers. If the condition is marketed in another country in a class of OTC drug products that may be sold only in a pharmacy, with or without the personal involvement of a pharmacist, it must be established that this marketing restriction does not indicate safety concerns about the condition's toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary to its use (section 503(b)(1)(A) of the act (21 U.S.C. 353(b)(1)(A))). If the restriction is related to such concerns, FDA would not consider this type of marketing to be similar to the broad OTC drug marketing in the United States, where products are marketed in a variety of outlets (e.g., grocery stores, convenience stores, drugstores), with no opportunity or requirement for professional consultation.

Proposed § 330.14(b)(2) would require that if the condition under consideration is marketed OTC in a foreign country, and its marketing in the United States is limited to prescription drug use, it would not be eligible for inclusion in an OTC drug monograph. FDA has determined that such a condition requires a prescription and cannot be considered GRAS/E for OTC use. Therefore, any request for OTC marketing status should be made under the NDA.

Proposed § 330.14(b)(3) would require OTC marketing for a minimum of 5 continuous years in the same country or countries and in sufficient quantity, as described in § 330.14(c)(2)(ii), (c)(2)(iii), and (c)(2)(iv). FDA is proposing these requirements to ensure that marketing is of sufficient duration to detect infrequent but serious adverse drug experiences (ADE's) that are occurring.

At this time, OTC drug monographs do not include timed-release formulations. These products are regulated as new drugs under § 310.502(a)(14) (21 CFR 310.502(a)(14)), and this document does not propose to change that status.

The agency is proposing a specific format for the submission of eligibility information to the agency. This format is intended for sponsors to provide specific information in a uniform manner to enable the agency to streamline the review process. Proposed § 330.14(c) describes the new time and extent application (TEA) sponsors would be required to submit when requesting consideration of a condition subject to this section. All of the information in proposed § 330.14(c)(1) through (c)(5) needs to be included in accordance with the procedures in proposed § 330.14(d). The information requested in § 330.14(c)(2), (c)(2)(i) through (c)(2)(iv), and (c)(3) is to be provided in a table format. If the condition is found eligible, then safety and effectiveness data would subsequently be submitted under the procedures proposed in § 330.14(f) and reviewed under the procedures in proposed § 330.14(g). If the agency initially determines that the condition can be considered safe and effective, then it will propose monograph status under the procedures in proposed § 330.14(g)(3).

Under proposed § 330.14(c)(1), sponsors must submit basic information about the condition that includes a detailed description of the active ingredient(s) or botanical drug substance(s), which are more fully described in § 330.14(c)(1)(i) and (c)(1)(ii), pharmacologic class(es), intended OTC use(s), OTC strength(s) and dosage form(s), route(s) of administration, directions for use, and the applicable existing OTC drug monograph(s) under which the condition would be marketed or the request and rationale for creation of a new OTC drug monograph(s). Proposed § 330.14(c)(1)(iii) allows reference to the current edition of the U.S. Pharmacopeia (USP)–National Formulary (NF) to help satisfy the requirements of the description of the active ingredient(s) or botanical drug substance(s).

Under proposed § 330.14(c)(2), sponsors must submit a list of all countries in which the condition has been marketed. This information is important to determine if the marketing experience is broad enough to ensure that an adequate safety profile exists.

Proposed § 330.14(c)(2)(i) would require sponsors to describe how the condition has been marketed in each country (e.g., OTC general sales direct-to-consumer; sold only in a pharmacy, with or without the personal involvement of a pharmacist; dietary supplement; or cosmetic). If marketed as an OTC pharmacy-only product, the sponsor must establish that this marketing restriction does not indicate safety concerns about the condition's toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary to its use (section 503(b)(1)(A) of the act). This information is important because diversity in the way products are marketed in other countries may indicate safety concerns that would be important to consider in determining suitability for OTC drug sale in the United States.

Proposed § 330.14(c)(2)(ii) would require sponsors to submit data on the number of dosage units sold in each country. Information presented should include: (1) The total number of dosage units sold, (2) the number of units sold by package sizes (e.g., 24 tablets, 120 milliliters (mL)), and (3) the number of doses per package based on the labeled directions for use. This information is important to FDA's assessment of the extent of marketing. This information is to be presented in two formats: (1) On a year-by-year basis, and (2) cumulative totals. The agency will maintain the year-to-year sales data as confidential, unless the sponsor waives this confidentiality. The agency will make the cumulative totals public should the condition be found eligible for consideration in the OTC drug monograph system.

Proposed § 330.14(c)(2)(iii) would require sponsors to adequately describe each country's marketing exposure (e.g., race, gender, ethnicity, and other pertinent factors) to ensure that marketing experience can be reasonably extrapolated to the U.S. population. Sponsors would have to explain any cultural or geographical differences in the way the condition is used in the foreign country and in the United States. The agency considers it important that OTC marketing experience be relevant to populations who would use such an OTC drug in the United States. The information in this paragraph need not be provided for OTC drugs that have been marketed for more than 5 years in the United States under an NDA.

Under proposed § 330.14(c)(2)(iv), sponsors must submit data on the condition's use pattern in each country, that is, how often it is to be used (according to the label) and for how long. If the use pattern varies in different countries based on the product's packaging and labeling, or if changes in use pattern have occurred over time, the sponsor must describe the use pattern for each country and explain why there are differences or changes. This information is important for evaluating whether the extent of use is adequate to detect infrequent but serious ADE's.

Proposed § 330.14(c)(2)(v) would require sponsors to describe each country's (where the condition is

marketed) system for identifying ADE's, especially those found in OTC marketing experience, including method of collection if applicable. The agency considers this information important to assess the ability of the system to detect ADE's that are occurring.

Under proposed § 330.14(c)(3), sponsors must submit a statement of how long the condition has been marketed in each country, accompanied by all labeling used during the marketing period, specifying the time period that each labeling was used. All labeling that is not in English must be translated to English, in accord with § 10.20(c)(2) (21 CFR 10.20(c)(2)). This information is important to determine whether the condition has been marketed for a material time and whether changes occurred in its labeling (e.g., formulation, warnings, and directions). The agency proposes that this information need not be provided for conditions that have been marketed OTC for more than 5 years in the United States under an NDA.

Under proposed § 330.14(c)(4), sponsors must submit a list of all countries where the condition is marketed only as a prescription drug and the reason(s) why its marketing is restricted to prescription in these countries. This information is useful because the same drug marketed OTC in one country may be limited to prescription in another country, and the agency is interested in knowing the reason(s) why its marketing is restricted to prescription in other countries.

Under proposed § 330.14(c)(5), sponsors must submit a list of all countries in which the condition has been withdrawn from marketing or in which an application for OTC marketing approval has been denied, and include the reasons for such withdrawal or application denial. This information is important to determine why other countries did not grant or withdrew OTC marketing status.

Under proposed § 330.14(c)(6), sponsors must provide the information in § 330.14(c)(2), (c)(2)(i) through (c)(2)(iv), and (c)(3) in a table format. This format is requested to provide for easy comparison of information from one country to another.

Proposed § 330.14(d) would require sponsors to submit three copies of the TEA, which would be handled as confidential until the agency makes a decision on the eligibility of the condition for consideration in the OTC drug monograph system. The TEA would be placed on public display in the Dockets Management Branch only if the condition is found eligible for consideration in the OTC monograph system. This procedure is necessary to allow sponsors to provide all pertinent eligibility information, some of which may be considered confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or section 301(j) of the act (21 U.S.C. 331(j)). Certain manufacturing information might be considered confidential. Year-to-year sales data would be considered confidential, but cumulative sales data over a period of years would not be considered confidential. Any proposed compendial standards would not be considered confidential. If the condition is not found eligible, the TEA will not be placed on public display, but a letter from the agency to the sponsor stating why the condition was not found acceptable will be placed on public display in the Dockets Management Branch.

Under proposed § 330.14(e), if a condition is found eligible, the agency would publish a notice of eligibility in the **Federal Register** and provide the sponsor and other interested parties an opportunity to submit data to demonstrate safety and effectiveness. The agency is proposing this two-step approach to: (1) Prevent sponsors from incurring unnecessary costs for developing safety and effectiveness data for a condition that may not meet basic eligibility requirements, (2) avoid expending agency resources evaluating safety and effectiveness data for a condition that does not meet the basic eligibility requirements, and (3) provide all other interested parties an opportunity to submit data and information on eligible conditions.

Under proposed § 330.14(f), the notice of eligibility will include a request for safety and effectiveness data to be submitted. Under proposed § 330.14(f)(1), sponsors must submit all data and information listed in § 330.10(a)(2) under the outline ''OTC Drug Review Information,'' items III through VII.

Under proposed § 330.14(f)(2), sponsors would be required to include all serious ADE's, as defined in §§ 310.305 and 314.80 (21 CFR 310.305 and 314.80), from each country where the condition has been or is currently marketed as a prescription drug or as an OTC drug or product. Sponsors would be required to provide individual ADE reports (Form FDA 3500A or a format that provides equivalent information) along with a detailed summary of: (1) All serious ADE's, and (2) expected or frequently reported side effects for the condition. Individual reports should be translated if not provided in English. Information derived from individual ADE reports is important in assessing safety, and expected or frequently reported side effects help identify information that should appear in product labeling.

Proposed § 330.14(g) describes the administrative procedures for FDA to use to evaluate the safety and effectiveness data. The agency could: (1) Use an advisory review panel to evaluate the safety and effectiveness data and make recommendations following the provisions of § 330.10(a)(3), (2) evaluate the data in conjunction with the advisory review panel, or (3) evaluate the data on its own without using an advisory review panel. These mechanisms provide the agency with flexibility in determining the most efficient method to evaluate data submissions consistent with the safety, effectiveness, and labeling standards in § 330.10(a)(4)(i) through (a)(4)(vi).

Under proposed § 330.14(g)(1), an advisory review panel may submit a report following the provisions of § 330.10(a)(5), or the panel may provide recommendations in its official minutes of meeting(s). This latter approach provides the agency with a mechanism to receive an advisory review panel's recommendations more quickly, and it eliminates unnecessary administrative burdens.

Under proposed § 330.14(g)(2), the agency may act on an advisory review panel's recommendations following the proposed revised procedures in § 330.10(a)(2) and (a)(6) through (a)(10). This approach provides the agency with a mechanism to be able to act on an advisory review panel's recommendations in a more expeditious manner. The agency is proposing to revise § 330.10(a)(6), (a)(7), and (a)(10) to incorporate these new procedures of placing an advisory review panels's recommendations on public display in the Dockets Management Branch and then acting on those recommendations.

Proposed § 330.14(g)(3) states that if the condition is initially determined to be safe and effective for OTC use in the United States, it will be proposed for inclusion in an appropriate OTC drug monograph(s), either by amending an existing monograph(s) or establishing a new monograph(s), if necessary.

Proposed § 330.14(g)(4) states how the agency will treat a condition that is initially determined not to be GRAS/E for OTC use in the United States.

Proposed § 330.14(g)(5) provides an opportunity for public comment on a proposal to include or exclude a condition and for publication of a final rule.

Proposed § 330.14(h) would permit marketing only under a final OTC drug

monograph(s) after the agency determines that the condition is GRAS/E and includes it in the appropriate OTC drug final monograph(s), and the condition complies with § 330.14(i). The agency is proposing this approach for several reasons: (1) It allows for thorough public consideration of any safety and effectiveness issues that might arise before marketing begins; (2) it allows for completion of compendial monograph standards for identity, strength, quality, and purity for all manufacturers to use; and (3) it allows manufacturers to avoid expensive relabeling when changes occur between the proposal and the final rule.

Under proposed § 330.14(i), any active ingredient or botanical drug substance included in a final OTC drug monograph must be recognized in an official USP–NF drug monograph, setting forth its standards of identity, strength, quality, and purity, prior to any marketing. The official USP–NF monograph should be consistent with the active ingredient(s) or botanical drug substance(s) used to establish general recognition of safety and effectiveness. The agency is proposing this compendial monograph requirement because the public availability of chemical standards would ensure that all OTC drug products contain ingredients that are equivalent to the active ingredients or botanical drug substances included in an OTC drug monograph. Inclusion in an official compendium of an ingredient's standards of identity, strength, quality, and purity would help ensure that OTC drugs are safe and effective for their intended uses. This USP–NF monograph requirement has been agency policy since 1989 (54 FR 13480 at 13486, April 3, 1989, and 54 FR 40808 at 40810, October 3, 1989).

After further considering how to best evaluate additional conditions that might be included in an OTC drug monograph, the agency's proposal in this document differs in a number of ways from the advance notice of proposed rulemaking. The agency is proposing certain new procedures for consideration of additional conditions in the OTC drug monograph system and amending existing OTC drug review procedures in § 330.10 to provide consistency with the use of these new procedures. The agency is proposing that a TEA containing certain information be submitted when a sponsor requests that an OTC drug initially marketed in the United States after the OTC drug review began in 1972 or an OTC drug without any U.S. marketing experience be considered for inclusion in an OTC drug monograph. Sponsors of additional conditions under these categories will be required to use these new procedures.

The agency will continue to use the existing OTC drug review procedures for conditions subject to the original OTC drug review. This includes: (1) Rulemakings that have not been completed to date (e.g., external analgesic drug products), (2) drug categories that were in the calls-for-data for OTC miscellaneous internal drug products (38 FR 31696, November 16, 1973, and 40 FR 38179, August 27, 1975) and for OTC miscellaneous external drug products (38 FR 31697, November 16, 1973, and 40 FR 38179, August 27, 1975) which the agency has not reviewed to date (e.g., urinary antiseptic drug products), and (3) drug categories that were not included in any of the calls-for-data but in which it can be unequivocally established that eligible products were marketed OTC before the OTC drug review began in 1972.

The new procedures will apply to all conditions marketed initially in the United States after the OTC drug review began in 1972 and all conditions for which the original OTC drug review has been completed but where sponsors want further consideration (e.g., a condition determined as nonmonograph in the original OTC drug review but for which additional data and information are now being presented). Sponsors of conditions in this last category will be required to follow the new procedures so that the agency can obtain the most recent marketing, safety, effectiveness, and compendial standard data and information available for the condition. In addition, because such conditions have been previously determined to be nonmonograph, no interim marketing would be allowed under existing procedures until the condition is included in a final monograph, which is consistent with newly proposed § 330.14(h).

The TEA will be handled as confidential, like the original submissions to an advisory review panel, until the agency makes a decision on the eligibility of the condition for consideration in the OTC monograph system. If the condition is not found eligible, the agency will notify the sponsor by letter, a copy of which will be placed in the Dockets Management Branch, and the TEA will not be placed on public display. If the condition is found eligible, the TEA will be placed on public display in the Dockets Management Branch, after deletion of information deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or section 301(j) of the act. Sponsors should identify such information and request that it be considered confidential under these provisions. The agency will publish a notice of eligibility in the **Federal Register** and provide the sponsor of the TEA and other interested parties an opportunity to submit data to demonstrate safety and effectiveness according to proposed § 330.14(f).

The agency will then evaluate the safety and effectiveness data, using the existing OTC drug review standards in § 330.10(a)(4)(i) through (a)(4)(vi). The agency may either convene an advisory review panel to assist in this evaluation or may elect to complete the evaluation alone. If a panel is used, a notice of meeting(s) will be published in the **Federal Register**, and the meeting(s) will be public. If the agency uses an advisory review panel, the panel may submit its recommendations to the agency in its official minutes of meeting(s) or in a separate report. These recommendations will be publicly available (in the docket). The agency will agree or disagree with the panel's recommendations, and proceed directly to a tentative order (notice of proposed rulemaking).

If the agency initially determines that a condition can be GRAS/E for OTC use in the United States, it will propose to include it in an appropriate OTC drug monograph(s). This will be done either by amending an existing monograph(s) or establishing a new monograph(s), if necessary.

If the agency initially determines that a condition cannot be GRAS/E for OTC use in the United States, it will notify the sponsor and other interested parties who submitted data by letter and place a copy of this letter in the Dockets Management Branch. The agency has used this ''feedback'' letter approach for many years during the ongoing OTC drug review, and it has resulted in the resolution of the monograph/nonmonograph status of many conditions prior to publication of a final determination in the **Federal Register**. The agency is proposing the letter approach as a way to provide early notification about the agency's scientific assessment of the data presented. The agency will publish a notice of proposed rulemaking to include the condition in § 310.502, which lists certain drugs determined by rulemaking procedures to be new drugs within the meaning of section 201(p) of the act (21 U.S.C. 321(p)). Interested parties will have an opportunity to submit comments and new data. The agency will subsequently publish a final rule (or reproposal if necessary) in the **Federal Register**.

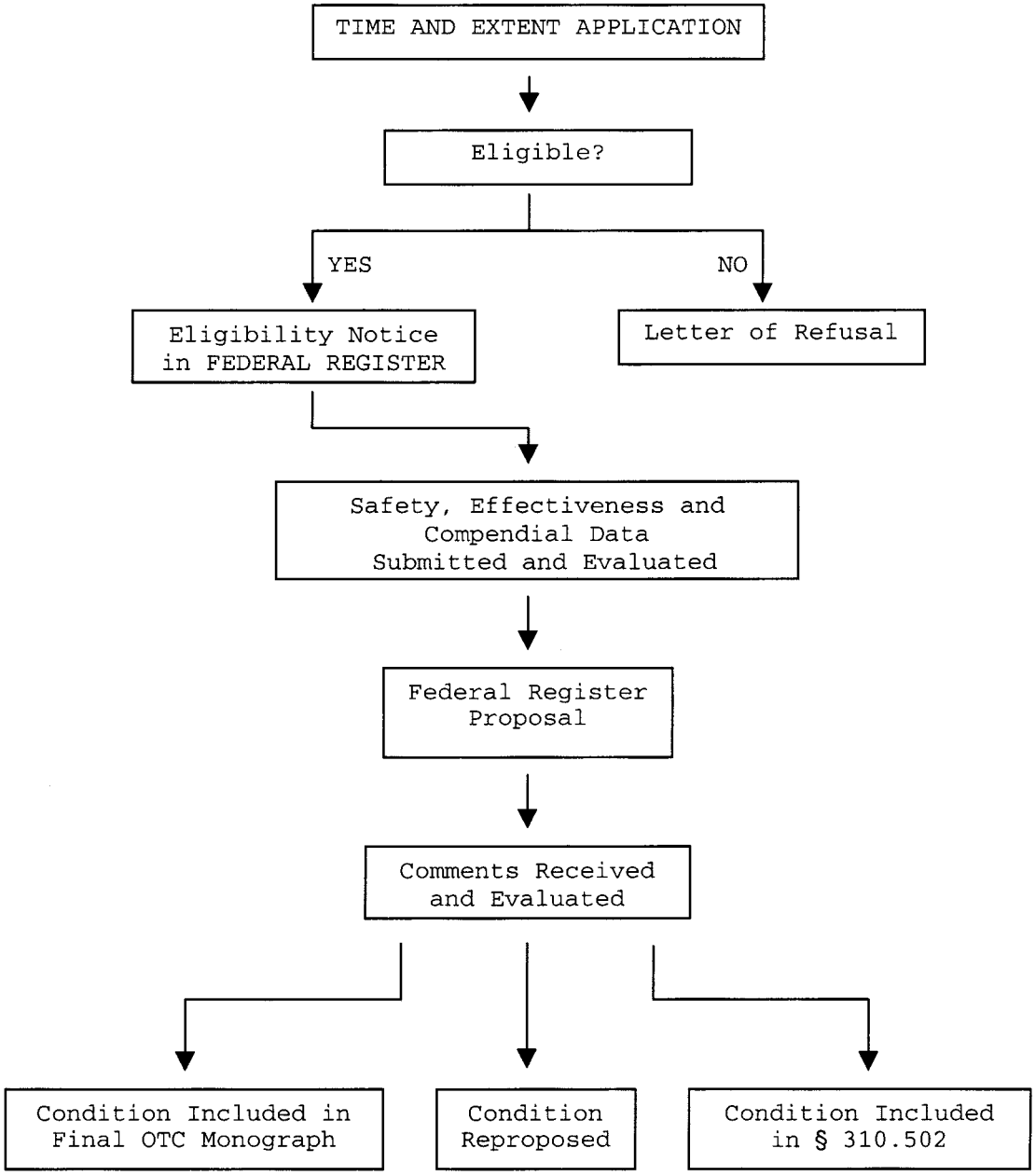
While the agency generally intends to use a two-step publication process for expediency, the agency may, in rare instances, elect to publish an advance notice of proposed rulemaking (three step process) when it needs to obtain additional public comment before determining whether to propose a regulation (see § 10.40(f)(3) (21 CFR 10.40(f)(3))).

The procedures for additional conditions in this proposal require that a compendial monograph exist for any ingredient included in an OTC drug monograph (a policy that has been in effect since 1989). Sponsors are encouraged to begin development of this compendial monograph at an early stage in the process. Therefore, the agency is proposing that sponsors include an official (if one exists) or proposed compendial monograph as an element of their safety and effectiveness data submission.

Once the agency publishes a proposal to amend or establish an OTC drug monograph to include a condition, it will then review the comments and publish a final rule (or reproposal if necessary) in the **Federal Register**. OTC marketing of the condition may begin when a final monograph is published.

The new procedures are outlined in the flow chart in Table 1 below.

TABLE 1.--PROPOSED NEW PROCEDURES IN § 330.14



These proposed new procedures are intended to streamline the process for additional conditions that will be evaluated. However, there are still some OTC drug rulemakings that need to be completed under the existing procedures.

Current § 330.10 sets forth the existing procedures for classifying OTC drugs as GRAS/E and not misbranded and for establishing monographs. FDA is proposing to amend § 330.10 to update some aspects of these procedures so that the existing procedures for the ongoing OTC drug review are consistent with the new proposed procedures.

The ''OTC Drug Review Information'' format and content requirements in § 330.10(a)(2) would be amended by revising items IV.A.3, IV.B.3, IV.C.3, V.A.3, V.B.3, and V.C.3 to add the words ''Identify expected or frequently reported side effects.'' after ''document case reports,'' and by adding new item VII to read:

VII. An official United States Pharmacopeia (USP)–National Formulary (NF) drug monograph for the active ingredient(s) or botanical drug substance(s), or a proposed standard for inclusion in an article to be recognized in an official USP–NF drug monograph for the active ingredient(s) or botanical drug substance(s). Include information showing that the official or proposed compendial monograph for the active ingredient or botanical drug substance is consistent with the active ingredient or botanical drug substance used in the studies establishing safety and effectiveness and with the active ingredient or botanical drug substance marketed in the OTC product(s) to a material extent and for a material time. If differences exist, explain why FDA is proposing these requirements for all conditions because this type of information will assist the agency in determining: (1) Appropriate warning statements, and (2) general recognition of safety and effectiveness by providing assurance that a proposed OTC active ingredient or botanical drug substance is consistent with the active ingredient or botanical drug substance formulation in the marketed OTC product(s) and the active ingredient or botanical drug substance used in establishing safety and effectiveness.

Current § 330.10(a)(5) describes the contents of the advisory review panel report on conditions considered for inclusion in an OTC drug monograph. The report includes 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 GRAS/E or would result in misbranding. FDA is proposing to amend § 330.10(a)(5)(ii) and (a)(5)(iii) by deleting the requirement that a statement of ''all'' active ingredients, labeling claims or other statements, or other conditions be included. FDA is proposing this revision because the statement ''all'' refers to an initial panel's review of an entire class of OTC drugs for inclusion in the OTC drug monograph system. Under the new procedures proposed in § 330.14, the agency may at times only consider one or more conditions for inclusion into an appropriate OTC drug monograph(s).

Current § 330.10(a)(6)(i) on proposed monographs, (a)(7)(i) on tentative final monographs, and (a)(9) on final monographs describe requirements affecting a category of OTC drugs. FDA is proposing to revise these paragraphs to add a provision for a specific OTC ingredient or ingredients as well as categories of drugs. These paragraphs would be revised by deleting the word ''is'' and adding the phrase ''or a specific or specific OTC drugs are.'' FDA is proposing these revisions because the agency may at times only consider adding one or more conditions to a designated category of OTC drugs.

Current § 330.10(a)(6)(iv) and (a)(12)(i) state that four copies of public comments must be submitted on a proposed monograph published in the **Federal Register**. FDA is proposing to reduce the number of copies to three because the fourth copy has proven to be unnecessary. FDA is also proposing to delete the phrase ''during regular business hours'' in § 330.10(a)(6)(iv) and replace it with ''between the hours of 9 a.m. and 4 p.m.''

FDA is proposing to revise § 330.10(a)(6)(iv) to permit the agency to place the advisory review panel's recommendations and the data it considered on public display in the Dockets Management Branch and publish a notice of their availability in the **Federal Register**, rather than publishing the panel's proposed monograph in the **Federal Register** as an ANPRM. FDA is proposing this revision to make recommendations available earlier. FDA may include this notice of availability as part of the tentative order under § 330.10(a)(7).

Current § 330.10(a)(7)(i) states that after reviewing all comments, reply comments, and any new data and information, the Commissioner of Food and Drugs (the Commissioner) shall publish in the **Federal Register** a tentative order containing a monograph establishing conditions under which a category of OTC drugs is GRAS/E and not misbranded. FDA is proposing to add the phrase, ''or alternatively, after reviewing a panel's recommendations'' to allow the agency to publish a tentative order at an earlier date. FDA is also proposing to change the 60-day comment period in § 330.10(a)(7)(i), (a)(7)(ii), and (a)(12)(i) to 90 days because the agency currently routinely provides 90 days for comment at these stages of an OTC drug monograph rulemaking.

Current § 330.10(a)(7)(ii) describes procedures for issuing a tentative order containing a statement of those active ingredients reviewed and proposed to be excluded from the monograph on the basis of the Commissioner's determination that they would result in a drug product not being GRAS/E or would result in misbranding. Currently, the Commissioner may issue such an order if no substantive comments in opposition to the panel report or new data or information were received by the agency. FDA is proposing to also allow publication of a tentative order when the Commissioner has evaluated and concurs with a panel's recommendation that a condition be excluded from the monograph. FDA is proposing this change to add another procedural option that the agency may use to speed up completion of a rulemaking.

Current § 330.10(a)(10)(i) and (a)(10)(iii) establish procedures for responding to requests for data and information to create an administrative record for use in proceedings under this section. FDA is proposing to add a new procedure for the submission of data by inserting in § 330.10(a)(10)(i) ''in response to any other notice published in the **Federal Register**.'' FDA is proposing this change to allow the agency to request data and information by publishing a notice in the **Federal Register** in addition to the other procedures because the agency may at times only consider one or more conditions to add to a designated class of OTC drug products and may not have the data reviewed and evaluated by an advisory review panel. FDA is proposing to insert the same language in § 330.10(a)(10)(iii) to correspond with the change in § 330.10(a)(10)(i).

Current § 330.13 describes conditions for marketing ingredients recommended for OTC use under the OTC drug review. The agency is adding new paragraph (e) to § 330.13 to state that it applies only to conditions under consideration as part of the OTC drug review initiated on May 11, 1972, and evaluated under the procedures set forth in § 330.10. Section 330.14(h) will apply to the marketing of all conditions under consideration using the additional criteria and procedures set forth in § 330.14.

III. Comments on the ANPRM

Sixteen comments were submitted in response to the ANPRM. Those comments and the agency's responses are summarized below.

A. Comments Related to Eligibility Criteria

1. Several comments agreed that the countries listed under section 802(b)(1) of the act (21 U.S.C. 382(b)(1)) are appropriate for obtaining relevant OTC marketing experience because their regulatory systems are at a level of sophistication similar to the system in the United States. Other comments opposed limiting marketing experience solely to these countries. One comment considered limiting marketing experience from select countries listed in the act for other purposes to be arbitrary. Another comment contended that it is the quality of the information, not the source, that should be controlling. Several comments contended that the proposed eligibility criteria should not limit marketing experience to that derived from Western European cultures. The comments stated that if valid data are available from a foreign source to make a determination of safe and effective use, those data should be accepted for consideration into the OTC drug monograph system, regardless of the particular country or countries involved. One comment added that while marketing in the section 802(b)(1) of the act countries is usually well defined, marketing in Latin America and much of Asia is increasingly as sophisticated.

One comment suggested that any country adopting and using the International Conference on Harmonization (ICH) format, criteria, and guidelines for ADE reporting and premarketing approval (NDA) safety documentation be considered for inclusion into section 802(b)(1) of the act. Another comment suggested that if any new countries are added to section 802(b)(1) of the act, marketing from these countries should automatically become acceptable for obtaining relevant OTC marketing experience.

The agency believes that conditions with relevant OTC marketing experience in section 802(b)(1) of the act countries would be more likely to succeed in meeting the criteria for consideration in the OTC drug monograph system because the marketing experience would be more like that in the United States and because the regulatory systems in those countries are similar to those in the United States. Similar marketing experience and regulatory controls should provide the agency more comparable information on which to base decisions.

Nonetheless, at this time, the agency sees no reason to limit marketing experience solely to section 802(b)(1) of the act countries. If manufacturers can provide the type of data described in § 330.14(c) from any foreign country, the agency will consider these data in making an eligibility determination.

2. Several comments stated that foreign marketing experience from the class of nonprescription drugs sold only in a pharmacy, with or without the personal involvement of a pharmacist, should qualify as OTC marketing. The comments contended that such experience is analogous to OTC drug marketing in the United States and that ingredients such as aspirin, acetaminophen, benzoyl peroxide, doxylamine, ibuprofen, and loperamide, for example, are all restricted to pharmacy-only sales in Europe. Several comments noted that a number of countries restrict some or all nonprescription drug products to pharmacy-only sales. Some comments suggested that the agency is misguided in its understanding of how drugs are distributed abroad. One of the comments pointed out that the determination of channels of distribution for OTC drugs largely differs in various countries because of different medical and pharmaceutical traditions. Another comment noted that the class of nonprescription drugs distributed for pharmacy-only sale, with or without the personal involvement of a pharmacist, is used for economic and cultural reasons and has become a method of protecting pharmacy competition, not a method of enhancing the public health. Some comments noted that in countries where OTC drug products are restricted to sale in pharmacies, sale of a drug product rarely involves actual advice and counsel by a pharmacist. One comment contended that the words ''prescription,'' ''OTC,'' and ''third class of drugs'' may describe different concepts from country to country. The comment concluded that the agency should not exclude data on foreign marketing experience on the basis of such artificial categories.

The agency recognizes that a number of countries have a class of nonprescription drugs required to be sold only in pharmacies with or without the personal involvement of a pharmacist, and that the reasons for this class of drugs may vary from country to country. The agency is concerned when this restriction is deemed necessary because a particular country considers intervention by a health professional necessary. While the agency has determined that it will consider marketing experience from this class of pharmacy-only sales, the sponsor needs to establish that this marketing restriction in a particular country does not indicate safety concerns about the condition's toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary to its use.

3. A number of comments stated that foreign cosmetic marketing experience should be accepted to support eligibility of marketing to a material extent and for a material time if the products are marketed in the United States as OTC drugs. Several comments noted that many topical product categories, for example, sunscreen, antiperspirant, dental, antidandruff, hair growth stimulants, and skin protectants, are regulated as cosmetics in Europe but classified as drugs in the United States. Two comments added that direct-to-consumer marketing of cosmetic products in foreign countries is substantially indistinguishable from OTC drug marketing in the United States and should be acceptable to satisfy the material extent/time requirements. One comment stated that the agency should consider dietary supplement marketing histories during the safety and effectiveness determination process. One comment argued that the statutory language and legislative history of section 201(p)(2) of the act do not limit ''use to a material extent and for a material time'' to use solely from products regulated as OTC drugs. The comment concluded that such a regulatory limitation would be in excess of the agency's grant of authority under the act and, therefore, in violation of the Administrative Procedure Act (APA).

The agency is aware that certain conditions regulated as OTC drugs in the United States may be regulated differently (e.g., as cosmetics or dietary supplements) in foreign countries. The agency does not wish to exclude these OTC conditions from consideration for inclusion in the OTC drug monograph system simply because they are regulated differently in various countries. When making an eligibility determination, the agency will consider any OTC condition that would be regulated as an OTC drug in the United States.

4. Three comments maintained that the agency should recognize the low level of risk associated with topically applied foreign OTC products and have more moderate regulatory requirements for these products in order to accelerate their availability in accordance with public health care needs. One comment argued that 5 years of marketing to demonstrate material time for topically applied foreign OTC products should automatically qualify them to be

marketed to a material extent. Another comment requested priority for products regulated as cosmetics in Europe if a final rule is not forthcoming in the immediate future.

The agency disagrees with the comments' suggestions. The agency does not find that there is automatically a low level of risk associated with products just because they are applied topically. The agency has identified concerns with a number of topically applied OTC active ingredients (e.g., benzoyl peroxide, coal tar, diphenhydramine, hydroquinone). While these concerns have not prevented OTC marketing, they do not allow for more moderate regulatory requirements or accelerated consideration of these conditions. Similarly, marketing of a topically applied foreign OTC product for 5 years or more does not assure that it has been marketed to a material extent nor that problems may not arise or exist. Some of the problems encountered with benzoyl peroxide, diphenhydramine, and hydroquinone became apparent only after years of OTC marketing in the United States. Therefore, the agency sees no reason to give priority specifically to topical products.

5. One comment requested clarification regarding the nature of marketing experience, including: (1) Whether a condition marketed OTC in one or more foreign countries would be deemed ineligible because of prescription marketing in other foreign countries, and (2) the agency's statement that it is ''essential that any prescription drug have some U.S. marketing experience before its OTC marketing is permitted in this country'' under an OTC drug monograph. The comment was concerned that the agency intends to disqualify foreign prescription drugs from OTC marketing in the United States under an NDA.

The fact that a condition is prescription in some foreign countries and OTC in others does not preclude its consideration for OTC status in the United States. In order to be considered in the OTC drug monograph system under this proposal, a condition would have to be marketed for OTC purchase in at least one country for a material extent and to a material time. However, broad OTC marketing experience in many different ethnic, cultural, and racial populations would help ensure that an adequate safety profile exists. The agency is proposing to require that sponsors provide a list of all countries where the condition is marketed as a prescription drug and a description of the reasons why the condition is not marketed OTC in these countries. This information would enable the agency to notify sponsors beforehand if specific safety data may be required in order to demonstrate that a condition is appropriate for marketing in the United States under an OTC drug monograph.

Concerning the comment that the agency intends to exclude foreign prescription drugs from switching to OTC in the United States under an NDA, this rulemaking does not prohibit or otherwise affect submission of an NDA for OTC marketing of a foreign prescription drug.

6. A number of comments agreed with the proposed 5-year minimum requirement to satisfy marketing for a material time. Two comments urged that the 5-year minimum marketing period be used as a guideline and not as a rigid requirement. The comments believed that 5 years of marketing would often be unnecessarily long for a condition whose extent of distribution is substantial. One comment stated that it was Congress' intent that a combination of total exposure from breadth and length of marketing provide assurance that the product is suitable for old drug status. The comment concluded that a mandatory minimum marketing period could be overly restrictive, particularly for OTC products that are used for limited treatment periods. One comment believed that a condition should be evaluated on the basis of the quality of data rather than on an arbitrary minimum 5-year marketing standard.

The agency has determined that the condition must be marketed both for a sufficient time and to a sufficient extent to detect infrequent but serious ADE's. Based on its experience with post marketing surveillance spontaneous reporting systems, the agency proposes that a minimum of 5 years of OTC marketing experience should be required to provide an appropriate margin of safety to ensure that marketing is of sufficient duration to detect infrequent but serious ADE's that are occurring. Additional parameters will be used to assess whether a condition has been marketed to a material extent (see proposed § 330.14(c)(3)(ii), (c)(2)(iii), and (c)(2)(iv)).

7. A number of comments agreed with the six proposed factors for determining marketing to a material extent. These proposed factors were as follows: (1) Number of dosage units sold; (2) number and types of ADE reports, and the requirements of the reporting system; (3) risks and consequences associated with the therapeutic category and indication; (4) use pattern (frequency: Occasional, acute, chronic); (5) potential toxicity (including dosage form and route of administration); and (6) history of use (i.e., use indications and exposures, including their toxicities). One comment stated that the third and fourth factors should only be applicable if an ingredient has been used for an indication that is not currently covered by the OTC drug monograph system. The comment claimed that the agency has made these assessments for indications already included in OTC drug monographs. The comment also stated that the fifth and sixth factors should be combined into a single factor. The comment contended that the agency has no need to review potential toxicity issues because it will be able to review actual toxicity based on widespread historical use. The comment recommended the creation of an additional factor, ''other general safety information.'' The comment stated that this factor could include safety information other than ADE reports, such as prescription ADE reports and consumer complaints regarding safety issues.

The agency has determined that certain of these factors pertain more directly to an evaluation of safety than to the determination of material extent and has decided to remove them from the list of factors used to determine material extent. The number and types of ADE reports, the risks and consequences associated with the condition, and toxicity information will now be addressed as part of the safety evaluation under proposed § 330.14(f). The agency is including the number of dosage units sold, the description of the ADE reporting system, the use pattern, and the history of use as part of the material extent determination. The number of dosage units sold is necessary to demonstrate if the condition's extent of use is sufficient to detect infrequent but serious ADE's that are occurring. The description of the ADE system is necessary to assess the ability of the system to detect ADE reports. Use pattern is necessary to determine if a product's use is different in other countries than it would be in the United States. Use indications and exposures are important to determine the scope of the condition's use.

8. Several comments stated that section 201(p)(2) of the act provides that an ingredient be used to a material extent or for a material time. The comments contended that the agency misinterprets the statutory language by requiring that a condition be marketed for both a material extent and a material time. These comments suggested that sponsors be granted the alternative of either complying with the material

extent or the material time criterion. Another comment disagreed with the approach of material extent and material time being two distinct entities. The comment recommended that a formula be developed that considers marketing to a material extent over marketing for a material time in order not to exclude an important health care solution based on marketing time alone. Two comments suggested that if a condition could only meet either the material extent or the material time criterion, a more stringent requirement to establish either material extent or material time be employed to compensate for the condition not meeting both criteria (e.g., require 10 years to demonstrate marketing for a material time instead of 5 years).

Section 201(p) of the act defines ''new drug'' as:

(1) Any drug * * * the composition of which is such that such drug is not generally recognized, among [qualified] experts * * * as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling * * *; or

(2) Any drug * * * the composition of which is such that such drug * * * has become so recognized, but which has not * * * been used to a material extent or for a material time under such conditions.

Section 201(p) of the act establishes two general parts to the ''new drug'' definition, joined by the conjunction ''or,'' both of which must be satisfied to escape ''new drug'' status. Similarly, within section 201(p)(2) of the act there are two criteria joined by ''or,'' both of which must also be satisfied to escape ''new drug'' status. As one appellate court has explained: ''Stated another way, a drug is *not* a ''new drug,'' and is therefore exempt from regulation under section [505(a)], only if such drug both (1) is generally recognized, among [qualified] experts * * *, as safe and effective for its labeled purposes; *and* (2) has been used to a material extent and for a material time'' (*United States* v. *Atropine Sulfate*, 843 F.2d 860, 861–62 (5th Cir. 1988)). See *USV Pharmaceutical Corp.* v. *Weinberger*, 412 U.S. 655, 660 (1973) (definition of ''new drug'' includes ''one that has not been used to a material extent and for a material time'').

This interpretation of section 201(p) of the act is also consistent with the Supreme Court's directive that the ''new drug'' definition must be liberally construed in order to effectuate the policy of the act to protect the public health and safety (*United States* v. *Article of Drug * * * Bacto-Unidisk*, 394 U.S. 784, 798 (1969)). Conversely, the situations in which a drug product is not a ''new drug'' are to be narrowly defined (*Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F.2d 795, 802 (2d Cir. 1980)).

Permitting a drug to drop out of regulation as a ''new drug'' without satisfying both the material time and the material extent prongs of section 201(p)(2) of the act would not satisfy the statute's underlying public health protection goal. For example, marketing a few units of a drug each year for many years would not provide enough information to ensure that infrequent but serious ADE's had been identified. Marketing many units of a drug for a very short period of time would be similarly inadequate to detect safety problems.

Accordingly, the agency disagrees with the comments. A condition that is considered ''not a new drug'' must satisfy both the material extent and the material time criteria in section 201(p)(2) of the act.

9. A number of comments suggested that the eligibility criteria should be flexible without rigid standards in specific areas. One comment contended that very specific criteria would reduce the eligibility of foreign marketing experience to an administrative effort, which would eliminate good judgment from the process. One comment contended that there should be no limitation on the type of marketing experiences that can be submitted. The comment added that sponsors should be permitted to provide evidence why the agency should consider certain marketing experience to be relevant. One comment stated that the agency should recognize that foreign marketing experiences may have many facets that are not necessarily less valid than those found in the United States. The comment contended that the eligibility criteria should be designed to equally and strictly apply to conditions that have been tested in a wide variety of foreign marketing experiences. The comment concluded that a rating system should be used, i.e., a low rating on one criterion could be compensated by a high rating on another criterion. Two comments suggested that the eligibility criteria be a guideline and not a rigid regulatory requirement. One comment requested the agency to provide specific eligibility criteria applicable to individual monographs rather than establish arbitrary criteria that may be irrelevant to particular categories of products.

The agency intends the proposed criteria and procedures to be a regulatory framework within which additional conditions will be evaluated for consideration in the OTC drug monograph system. The criteria are intended to be general in nature and to provide the agency flexibility and allow the use of judgment in evaluating eligibility requests. While any marketing experience can be submitted, sponsors will have to convince the agency that some experiences are relevant and appropriate, even though different from U.S. marketing experience. However, the agency intends to apply the criteria and use its judgment in specific situations. The agency may well use its judgment to balance a lower rating on some criteria with a higher rating on other criteria. The agency sees no need to provide specific eligibility criteria for each monograph. The agency considers the general criteria adequate and appropriate for all of the OTC drug monographs. In conclusion, the criteria and procedures provide a regulatory framework within which to apply judgment and be flexible as appropriate and necessary in considering additional conditions for inclusion in the OTC drug monograph system.

B. Comments Related to Safety and Effectiveness Evaluation

10. A number of comments recognized the usefulness of assessing ADE's that have occurred during marketing as an important element in assessing the safety of a condition. Some comments added that the existence of an ADE reporting system in a foreign country is a factor in evaluating the relevance of the marketing experience, while several comments suggested that the absence of a mandatory ADE reporting system should not preclude a condition from being eligible in the OTC drug monograph system. Several comments argued that the absence of a mandatory ADE reporting system should not be determinative of safety, but should be only one factor when determining eligibility. Two comments stated that it is the reliability and scope of the ADE data collection system that is important, not the form of availability. Several comments noted that there is no mandatory ADE reporting system currently in place for OTC drug products in the United States and the OTC drug monograph system currently includes hundreds of ingredients that have never been subject to mandatory ADE reporting. One comment added that over a period exceeding 5 years, even in the absence of a mandatory reporting system, serious safety problems would be identified in European and other countries with adequate regulatory oversight and sophisticated health care systems. The comment stated that literature reports of experience in hospitals, poison control centers, clinical studies, etc., and data from voluntary reporting channels

provide a mechanism for gathering sufficient information to determine whether a serious safety problem exists. Several comments suggested that mandatory ADE requirements for foreign marketed conditions would establish a dual standard, with a more rigorous standard for evidence of safety being placed on foreign marketed conditions than exists for U.S. OTC drug products.

One comment mentioned that many U.S. OTC drug products are regulated as cosmetics or dietary supplements in other countries and would not be subject to ADE reporting requirements. Another comment suggested that the agency should assess foreign ADE reporting systems only after it has defined the parameters for a suitable OTC ADE reporting system in the United States. Another comment suggested listing elements of ADE reporting systems in order to generate an overall rating of each country's monitoring system. Two comments stated that it is unrealistic and unnecessary for the agency to require ADE reports from every country where an ingredient is marketed. One comment requested clarification of the term ''important'' ADE. One comment claimed that due to sporadic or sparse marketing, not every country will provide useful data. The other comment noted that some companies market products in more than 100 countries and should only concentrate on sophisticated countries with OTC sales. The comment supported a requirement that sponsors provide all relevant and significant ADE's of which they are aware. The comment noted, however, that in most countries, a company is not authorized to obtain ADE reports for a competitor's product.

One comment stated that the agency should only request ADE reports associated with nonprescription drug marketing. Another comment maintained that when the dosages are similar between prescription and OTC drug uses, priority should be given to the collection of OTC ADE reports. One comment stated that a contradiction exists between the agency's acceptance of foreign prescription drugs' ADE reports and the agency's belief that foreign marketing as a prescription drug should not be part of the criteria for determining material extent and material time.

The agency considers ADE information to be crucial in assessing the safety of a condition for inclusion in an OTC drug monograph. The agency acknowledges that a mandatory ADE reporting system for monographed OTC drug products is currently not in place in the United States, but the agency plans to propose the creation of such a system in the near future. The agency is also aware that such a system does not exist in many industrialized countries. Nonetheless, many countries have a drug marketing approval process and a postmarketing surveillance system that can identify ADE's. The system that exists needs to detect ADE's that are occurring, i.e., both: (1) Serious ADE's and (2) expected or frequently reported side effects for the condition. This information enables the agency to assess the risks of using the condition OTC and to label the product informatively for consumers.

As one comment mentioned, literature reports on experiences in hospitals, poison control centers, clinical studies, and other similar settings, plus data from voluntary reporting channels, provide information for assessing a condition's safety. It will be the sponsor's burden to provide this information to the agency to support OTC safety. The agency points out that this type of information is similar to the information manufacturers have routinely been requested to submit for drugs evaluated under the OTC drug review. Safety information under the OTC drug review procedures (§ 330.10(a)(2)) includes controlled studies, documented case reports, pertinent marketing experiences that may influence a determination as to the safety of each individual active ingredient, and pertinent medical and scientific literature. Thus, this type of information is routinely considered as part of the condition's safety evaluation.

The agency also considers it very important to have this ADE information provided from every country where the condition is marketed. This information will be helpful to address some of the ethnic, cultural, and racial variances that may exist among users as well as to provide a broad marketing background more relevant to the U.S. population. The agency considers this information useful even from countries with sporadic or sparse marketing, or where the condition has been withdrawn. Therefore, the agency is requiring that sponsors include all of this marketing experience as relevant information of which they are aware. This requirement applies equally to conditions regulated as cosmetics or dietary supplements in foreign countries, but which would be regulated as OTC drug products in the United States. If there is no mandatory ADE reporting system for such products in the foreign country, the sponsor can still provide information from the scientific literature and information obtained from voluntary reporting channels. This would also include such information for a competitor's product if available in the scientific literature or other public sources (e.g., news articles, press releases).

The agency believes that prescription as well as OTC ADE reports for the condition should be evaluated. Prescription ADE reports may provide useful information to evaluate safety for U.S. marketing under an OTC drug monograph. In addition, ADE reports associated with the other doses (higher or lower) or different indications associated with the product marketed as a prescription drug would be useful for assessing the safety margin for OTC use. The agency finds no contradiction in requesting prescription ADE reports for this purpose.

The agency sees no benefit in trying to rate each country's monitoring system. As one comment noted, the reliability and scope of the data are the important factor. Nor does the agency see a need to wait until its OTC ADE reporting system for monographed OTC drugs is fully defined. The type of ADE information the agency is requiring is similar to the information manufacturers have routinely been requested to submit for drugs evaluated under the OTC drug review.

The agency concludes that ADE information is a critical factor in assessing the safety of a condition for inclusion in an OTC drug monograph. However, the agency believes that ADE reports are more appropriate as part of the assessment of safety, rather than as part of establishing eligibility. The agency is proposing new § 330.14(f)(2) to require the submission of the following: (1) All serious ADE's, as defined in §§ 310.305 and 314.80, as elements of required ADE reporting to support a foreign condition's safety, and (2) expected or frequently reported side effects that may be important for consumer product labeling.

11. Several comments objected to the agency's position that foreign marketing exposure would have to be described sufficiently to ensure that the condition can be reasonably extrapolated to the U.S. population. Some comments contended that, because the United States has a wide range of ethnic, cultural, racial, and foreign populations comparable to many countries, it is improper and unjustified to emphasize the comparability of foreign and U.S. populations as a determinate factor. One comment noted that it is usually assumed (absent unusual circumstances) that any drug, whether marketed in the United States under an NDA or OTC drug monograph, is suitable for use by the entire population.

Several comments added that the agency has never solicited race, gender, or ethnicity marketing information for a condition in the OTC drug review, nor is there a requirement under an NDA for testing a condition in any particular demographic group. One comment suggested that for the agency to determine that foreign products in general and European products in particular present some significant cultural risk would be an unlawful nontariff trade barrier in violation of the General Agreement on Tariffs and Trade (GATT) and the North American Free Trade Agreement (NAFTA). Another comment mentioned that marketing in Latin America and much of Asia is also very relevant. Two comments stated that they would support less rigid requirements. One of these comments supported a requirement that companies disclose any concerns they are aware of regarding medical, cultural, or genetic issues.

The agency recognizes that the United States has a wide range of ethnic, cultural, racial, and foreign populations. The agency believes that when a condition is included in an OTC drug monograph, there should have been broad OTC marketing experience in many different ethnic, cultural, and racial populations to assure that a sufficient profile of the condition exists. For example, a sunscreen drug product with a marketing history only in a Latin American country may not have a sufficient marketing history to allow extrapolation to the full range of skin types of the U.S. population. Likewise, an antacid, cholesterol lowering drug, or vaginal contraceptive with marketing experience only in an Asian country may not have a sufficient profile for extrapolation to the entire U.S. population because of dietary and cultural differences between the countries' populations.

While the agency may not routinely solicit race, gender, or ethnicity ''marketing'' information for a drug in the OTC drug review, the agency considers this one of the parameters that appropriately can be assessed to evaluate material extent. The agency has considered this parameter in developing certain OTC drug monographs. For example, issues related to unique racial characteristics have arisen in considering OTC skin bleaching drug products. In evaluating a protocol for a plaster dosage form containing counterirritant ingredients, which had a marketing history primarily in an Asian population, the agency informed the manufacturer that skin from subjects with different ethnic backgrounds should be studied. The agency stated that as much data as possible was needed to provide support for the product, and the protocol should include a diverse population regarding age, sex, and race (Ref. 1).

In conclusion, the agency considers it important that OTC foreign marketing experience be relevant to populations targeted for marketing in the United States. Therefore, the agency is requiring that, as part of the TEA, sponsors sufficiently describe the condition's foreign marketing experience to fully support extrapolation to U.S.-targeted populations. Sponsors may use the categories and definitions in The Office of Management and Budget's **Federal Register** notice, titled ''Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity.'' The notice identifies six combined racial and ethnic categories (1. American Indian or Alaska Native, 2. Asian, 3. Black or African American, 4. Hispanic or Latino, 5. Native Hawaiian or Other Pacific Islander, and 6. White (62 FR 58781, October 30, 1997)).

C. Comments on Administrative Procedures

12. Several comments supported the agency's proposed two-step application process. One comment requested clarification on several aspects of the process: (1) Who within the agency would be responsible for reviewing the eligibility submission, (2) the content and format for eligibility and data submissions, and (3) the agency's regulatory timeline for reviewing submissions. Several comments requested the agency to establish regulatory timelines for each step of the review process. Three comments recommended that the agency establish a 90-day time period for the review of eligibility data. Two comments requested that this time period be 120 days. Three comments recommended that the agency establish a 1-year timeline for reviewing safety and efficacy data. Two comments requested that, within the review periods, the agency give regulatory priority to conditions that uniquely meet Americans' health needs.

The agency's Division of OTC Drug Products will be responsible for evaluating all TEA's. The agency does not anticipate establishing specific timelines for the review of the TEA or data submissions for safety and effectiveness due to differences that may exist in the quantity and quality of submissions. The agency is concerned that, in the initial period of time following the publication of a final rule, there may be substantial numbers of submissions that will require handling and evaluation by the agency. The agency considers it desirable to implement procedures that will streamline this process to ensure that agency resources are used appropriately and result in timely action on submissions.

In reviewing data submissions on safety and effectiveness, the agency intends to use both internal and external resources, as appropriate. The agency may request submission of data and information for conditions in specific pharmacological classes (e.g., drug categories listed in § 330.5) and/or certain indications during specified time periods so that an entire class of conditions (e.g., foreign sunscreen ingredients) can be reviewed at one time. The agency believes that there may be other options for streamlining this review process and invites specific comments on these matters.

13. One comment urged the agency to combine its two-step application process into one unified process. The comment contended that each of the two steps involves consideration of the same information and, therefore, should be combined. The comment concluded that a two-step application process would take twice as long as a single simplified process. One comment objected that the agency had not sufficiently distinguished between the eligibility of drug conditions for inclusion in the OTC drug monograph system and the evaluation of whether such conditions are GRAS/E. The comment argued that the initial eligibility determination should not intrude on the separate safety and effectiveness evaluation.

Another comment contended that FDA's proposed eligibility process is inconsistent with the statutory language of section 201(p) of the act. The comment argued that section 201(p)(1) and (p)(2) of the act provides two independent criteria for finding that a product is not a new drug, but that the agency's proposal makes the material extent and material time criteria of section 201(p)(2) of the act part of the safety and effectiveness requirement of section 201(p)(1) of the act. The comment added that FDA's proposal prevents separate and independent consideration by interpreting the material extent and material time requirements to be evaluated by data that relate properly to the safety of the product. The comment contended that FDA's proposed procedure uses the material extent and material time requirement as an initial screen to exclude drugs from the OTC drug monograph system. The comment

contended that this interpretation of the act is unsupported by the plain language, judicial interpretations, or legislative history of the act, and the agency's past and current OTC drug review practices. The comment concluded that the agency's approach results in arbitrary and capricious action under the APA (5 U.S.C. 706(2)(A)).

The agency believes that a two-step application process is the most efficient and appropriate method for it to determine whether a condition is acceptable for inclusion in the OTC drug monograph system. The agency is proposing this two-step approach to: (1) Prevent sponsors from incurring unnecessary costs for developing safety and effectiveness data for a condition that may not meet basic eligibility requirements, (2) avoid expending agency resources evaluating safety and effectiveness data for a condition that does not meet the basic eligibility criteria, and (3) provide all interested parties an opportunity to submit safety and effectiveness data and information.

Based on the comments and a consideration of the options raised in the ANPRM, the agency has decided that a number of the criteria initially proposed as part of an eligibility determination should now be part of the safety determination (see section III.A, comment 8 of this document). The agency believes that this approach would provide for a separate and expedited consideration of both elements and would not result in a protracted process.

14. One comment requested that the agency make all positive eligibility determinations publicly available so that all interested parties would have a chance to submit safety and effectiveness data and information.

The agency agrees with this comment. If the condition is found eligible, the agency will publish a notice of eligibility in the **Federal Register** and provide the sponsor and other interested parties an opportunity to submit data to demonstrate safety and effectiveness.

15. Two comments stated that once the agency determines that a condition is GRAS/E, it should be incorporated into a new or existing monograph by the proposed rule/final rule publication procedure in the **Federal Register**. One comment contended that the original three-step publication procedure (i.e., advance notice of proposed rulemaking, tentative final monograph, final monograph) used in the OTC drug review is no longer justified due to the absence of advisory review panels. The comment concluded that in this case where FDA would be making a safety and effectiveness determination, a two-step procedure would be sufficient and appropriate.

The agency generally agrees with the comments that the original three-step publication process is no longer needed to make a determination that an additional condition being added to the OTC drug monograph system is GRAS/E. However, the agency may use outside experts as part of the review process. These experts could review the safety and effectiveness data and provide recommendations to the agency. The agency will make those independent recommendations public by placing them in the docket, evaluate the data and recommendations, and then publish a notice in the **Federal Register**. The agency may elect to expedite the review process by evaluating the data in conjunction with the advisory review panel or outside experts. If the agency concurs with the experts' recommendations to include a condition in a monograph, the agency will publish a notice of proposed rulemaking to amend an existing monograph(s) or create a new monograph(s).

If the agency agrees with the experts' recommendation not to include a condition in a monograph, it will inform interested parties by letter and place a copy in the Dockets Management Branch. Subsequently, the agency will publish a notice of proposed rulemaking in the **Federal Register** providing a summary of the experts' recommendations and proposing to include the condition in § 310.502. The agency will provide interested parties an opportunity to submit comments and new data, and will subsequently publish a final rule in the **Federal Register**.

In conclusion, the agency generally intends to use a two-step publication process for conditions that are evaluated under this notice. However, the agency may elect to publish an ANPRM to obtain public comment before publishing an actual notice of proposed rulemaking (see § 10.40(f)(3)).

D. Comments on Marketing Policy

16. Several comments objected to the agency's proposed marketing policy. The comments stated that interim marketing should be authorized after the agency determines a condition is eligible for consideration in the OTC drug monograph system. One comment contended that similar standards in the ''rush to market rule,'' codified in § 330.13, should apply for foreign OTC drugs and products. The comment noted that this rule allowed OTC drug ingredients that were lawfully marketed before May 11, 1972, in the United States to be marketed prior to a final evaluation by the agency. Two comments contended that the agency's proposed marketing policy was inconsistent with its current policy permitting the marketing of Category III (more safety and/or effectiveness data needed) conditions that have insufficient evidence of safety or effectiveness. Two comments stated that the agency's proposed marketing policy was inconsistent with its initiatives to harmonize drug regulations by creating an unfavorable bias towards foreign products. Two comments argued that by accepting 5 years of marketing experience from countries listed in the Export Reform Act of 1996 (Public Law 104–134), the agency should trust that the exposure to unnecessary risk would be minimal, thereby alleviating the need for a different interim marketing policy for foreign products. One comment disagreed with the agency statement that allowing any condition to be marketed before it was evaluated for safety and effectiveness would subject the public to ''unnecessary risk.'' The comment contended that the minimum level of risk for many products, in particular topical and sunscreen drug products, does not support a blanket prohibition of interim marketing based on risk. The comment argued that there is no scientific or legal justification for such an approach. The comment noted that skin cancer is a serious and growing health problem, and risks of keeping new sunscreen products from the American public outweigh the risk of making them available. The comment recommended that the agency adopt a more flexible interim marketing policy that recognizes the low-level risks of certain therapeutic categories/conditions.

The agency's proposed marketing policy in § 330.14(h) would allow marketing only after a condition is included in an applicable final OTC drug monograph(s). Many of the conditions that may be submitted will not have been marketed previously to the U.S. population. Therefore, the agency considers it important that there be thorough public consideration of any safety and effectiveness issues that might arise before marketing begins. Interested parties and persons with specific knowledge about the condition may offer useful comments and suggestions regarding the OTC marketing of the condition. If there are controversial issues regarding OTC status, the agency does not want interim marketing to occur while these issues are being resolved. If there are no controversial issues, then the period of time between the proposal and the final

rule to add a condition to a monograph will generally be short.

For reasons stated above, the agency is not using the marketing policy in §§ 330.13 and 330.10(a)(6)(iv) (Category III conditions) for additional conditions to be considered for inclusion in the OTC drug monograph system. These sections were intended to apply to active ingredients marketed in the United States prior to the beginning of the OTC drug review. The current proposal applies to OTC drugs initially marketed in the United States after the OTC drug review began in 1972 and OTC drugs without any U.S. marketing experience.

The agency acknowledges that some ingredients may have what some people consider a minimal level of risk. As discussed earlier, many topical conditions raise concerns that require agency evaluation before marketing may begin. In some cases, special conditions (e.g., label warnings) may be necessary for marketing. In the case of sunscreens, the agency has evaluated substantial safety data (e.g., primary irritation potential, phototoxicity, photosensitization) before proposing several sunscreen ingredients for inclusion in the sunscreen monograph. Thus, the agency has determined that topical and sunscreen drug products should not qualify for a different status based on the nature of the products.

E. Comments on Compendial Monograph Requirements

17. Several comments stated that the agency should recognize all national and international compendia. One comment interpreted ''official compendia'' to mean not only the USP, but also the European Pharmacopeia and pharmacopeias from the export countries identified in section 802(b)(1) of the act. Another comment expressed concern that the USP may be delayed in establishing herbal monographs due to the chemical complexity of plant ingredients. The comment suggested that the agency accept a compendial monograph from the European Pharmacopeia or pharmacopeias from the export countries as long as the development of a USP monograph is being pursued. One comment stated that requiring only single ingredients to be recognized in an official compendium would be too narrow an approach.

The proposed rule would require an official USP–NF drug monograph for the active ingredient(s) or botanical drug substance(s). These compendia recognize monographs for both single ingredient and botanical products where appropriate. Although the USP–NF does not presently recognize foreign compendial monographs, it does review foreign compendial monographs on a case-by-case basis to determine if they can be used in developing a USP–NF monograph. However, the agency would not recognize a foreign compendial monograph until USP–NF determined it was acceptable and incorporated it into an official drug monograph.

The USP–NF is currently taking steps to facilitate international commerce and product registrations. USP–NF recently proposed a new general chapter 13, ''Concordance of Foreign Pharmacopeial Tests and Assays'' (Ref. 2). This chapter would allow alternative tests and assays established by the European Pharmacopeia and the Pharmacopeia of Japan to demonstrate that an article meets USP standards. As international harmonization progresses, USP states that it will also consider the applicability of other pharmacopeias. The agency notes that while the USP proposal rests on a presumption that articles of acceptable quality can emerge where they are produced in accordance with recognized principles of good manufacturing practice and foreign official methods of analysis, USP requires that its General Committee of Revision examine each test or assay with a view to acceptable concordance with the USP test or assay. USP also cautions that these individual determinations of concordance are made solely and independently by USP; no corresponding provision or lack thereof by another pharmacopeia is to be presumed (Ref. 2).

18. Two comments objected to the agency's requirement that a USP monograph be in place before FDA allows any interim marketing. The comments stated that a USP monograph should be in place at the time an OTC drug final monograph is completed.

As discussed in section III.D, comment 16 of this document, the agency is not proposing to allow any interim marketing. The agency agrees that a compendial monograph should be in place when an ingredient is included in a final monograph. It has been agency policy since April 3, 1989 (54 FR 13480 at 13486) that before any ingredient is included in a final OTC drug monograph, it must have a compendial monograph. That monograph sets forth the identity, strength, quality, and purity of the drug substance and drug products made from the drug substance and would include, for example, specifications relating to stability, sterility, particle size, crystalline form, and analytical methods. If necessary, the agency will require additional compendial standard criteria in the OTC drug final monograph based on the data that support generally recognized safe and effective status. A compendial monograph helps ensure that OTC drug products contain ingredients that are equivalent to active ingredients or botanical drug substance(s) included in OTC drug monographs. This requirement will also encourage interested sponsors to work with USP to develop a compendial monograph as expeditiously as possible.

F. General Comments

19. One comment urged the agency to issue a final rule, rather than a proposed rule, as the next step in this rulemaking. The comment stated that there had been a considerable delay since it submitted its petition, and contended there is no legal requirement or administrative need for FDA to first issue a proposed rule. The comment concluded that if FDA issues a proposed rule, it should provide a 60-day comment period and issue a final rule within 120 days. Another comment urged the agency to move forward promptly on this rulemaking and to begin accepting petitions for additional conditions in the OTC drug monograph system upon publication of the proposed rule.

The agency disagrees with the comments' suggestions. In order to solicit a broad range of comments on the approach FDA was considering on eligibility for consideration under the OTC drug monograph system, the agency published an ANPRM. Under the agency's procedural regulations in § 10.40(f)(3), FDA may publish an ANPRM to request information and views on a matter from the public before it decides to publish a proposed rule. Having considered the comments submitted in response to this ANPRM, the agency believes it is now appropriate to propose specific revisions to the codified text of its current OTC drug monograph system regulations and to solicit comments on these specific revisions. The agency is providing a 90-day comment period, rather than the 60 days as suggested by the comment, because it anticipates that most interested parties will want a longer period of time to respond to the criteria and procedures proposed in this document, and the agency wishes to avoid requests for an extension of the comment period.

The agency also disagrees that it would be efficient to begin accepting petitions for additional conditions upon publication of the proposed rule. FDA's consideration of the comments in response to this proposed rule may result in changes to the proposed requirements. Encouraging submissions following the proposal before the final

rule issues may result in considerable wasted and inefficient efforts by sponsors and by agency employees. The agency intends to move expeditiously to consider the comments and develop a final rule after the close of the comment period.

20. One comment requested clarification whether the final regulation would apply to the review of any condition proposed for inclusion in a final, pending, or newly proposed OTC drug monograph. The comment stated that this approach would ensure that a condition currently being considered for inclusion in an OTC drug monograph will be reviewed by the same standards as a condition reviewed after finalization of the proposed rulemaking. Another comment asked the agency to confirm that it will consider ingredients marketed in foreign countries for OTC indications that are not currently covered by existing OTC drug monographs.

This rulemaking addresses how OTC marketing experience in the United States or other countries could be used to qualify additional conditions for consideration under the OTC drug monograph system. Once found eligible, whether for a final, pending, or newly proposed OTC drug monograph, the condition will be reviewed using the same OTC drug standards in § 330.10(a)(4) that have been used throughout the OTC drug review process. The agency has included such a provision in proposed § 330.14(g). Conditions not covered by existing OTC drug monographs will be considered under this proposal.

21. One comment noted that the agency did not differentiate between the various dosage forms under its definition of ''conditions.'' The comment stated that it interpreted ''dosage form'' to mean that immediate-release, solid oral dosage forms (e.g., tablets) and liquid oral dosage forms (e.g., drops or syrups) were grouped together, with no further differentiation being made. Another comment contended that if an ingredient intended for oral ingestion is approved for marketing, manufacturers should be able to include the ingredient in a variety of oral, immediate-release dosage forms, such as, tablets, capsules, or liquids. The comment added that the same principle should apply to topical ingredients. The comment mentioned that when the agency evaluates ingredient eligibility, it should not require 5 years of marketing for each dosage form.

Most OTC drug monographs do not limit the dosage forms for listed ingredients. One exception is timed-release formulations. These products are regulated as new drugs under § 310.502(a)(14). In some cases, there are other reasons to limit allowable dosage forms or dosage forms that have specific requirements. For example, the agency discussed dosage forms (vehicles) for topical drug products when it amended the external analgesic tentative final monograph to include 1 percent hydrocortisone (55 FR 6932 at 6947 and 6948, February 27, 1990). The agency expressed concerns about 1 percent hydrocortisone being incorporated into a dosage form that would increase absorption through the skin, thus creating the possibility of an increased safety risk.

While most OTC drug monographs will not limit dosage forms, there may be specific situations where it is necessary to require 5 years of marketing experience for a novel or special dosage form.

IV. Legal Authority

FDA's proposal to amend its regulations to include criteria for additional conditions and procedures for classifying OTC drugs as GRAS/E and not misbranded is authorized by the act. Since the passage of the act in 1938, submission of an NDA has been required before marketing a new drug (section 505 of the act (21 U.S.C. 355)). Section 201(p) of the act defines a new drug as:

> (1) Any drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, * * *; or
>
> (2) Any drug * * * the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

To market a new drug, an NDA must be submitted to, and approved by, FDA before marketing. Only drugs that are not new drugs may be covered by an OTC drug monograph. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act. Under part 330, FDA's regulations outline the requirements for OTC human drugs that are GRAS/E and not misbranded. Proposed § 330.14 adds additional requirements.

V. Proposed Implementation Plan

FDA proposes that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**. After that date, the agency will begin accepting TEA's.

VI. Requests for Comments

Interested persons may, on or before March 22, 2000, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Written comments on the information collection requirements may, on or before January 19, 2000, be submitted by interested persons to the Office of Information and Regulatory Affairs, OMB (address above). Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments 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. Written comments received regarding this proposal may be seen by interested persons in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; and distributive impacts and equity). Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires an analysis of regulatory options that would minimize any significant economic impact of a rule on small entities. The Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this rule is consistent with the pronciples set out in the Executive Order and in these two statutes. OMB has determined that the proposed rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Because this rule does not impose any mandates on

State, local, or tribal governments, it is not a significant regulatory action under the Unfunded Mandates Reform Act. Although the agency does not believe that this rule will have a significant economic impact on a substantial number of small entities, there is some uncertainty with respect to the estimated future impact. Thus, a regulatory flexibility analysis is presented below.

A. Regulatory Benefits

The purpose of the proposed rule is to establish criteria and procedures for classifying OTC drugs as GRAS/E and not misbranded. Currently, a sponsor wishing to introduce into the United States an OTC drug condition marketed solely in a foreign country must prepare and submit an NDA. Likewise, companies with OTC drugs initially marketed in the United States after the 1972 initiation of the OTC drug review must have an NDA. This proposed rule provides procedures for these NDA drugs to become eligible for inclusion in the OTC drug monograph system by first submitting a TEA to show marketing ''to a material extent'' and ''for a material time.'' Once determined eligible, safety and effective data would be submitted and evaluated. The agency is proposing the two-step process to allow sponsors to demonstrate that eligibility criteria are met prior to requiring the expenditure of resources to prepare safety and effectiveness data.

The flexibility to obtain U.S. marketing approval through FDA's OTC drug monograph system will provide an overall net benefit to the companies seeking these approvals, as well as to the American public. One important benefit to sponsoring companies would be the saving of NDA user fees. The Prescription Drug User Fee Act (section 736 of the act (21 U.S.C. 379h)) requires a one-time application fee for each NDA submitted, and yearly product and establishment fees, as applicable, for each NDA approved. In 1998, these fees were $256,846 (applications with clinical data), $18,591, and $141,966 respectively. Therefore, one-time user fees of $256,846, and ongoing fees of up to $160,557 ($18,591 + $141,966) would be avoided if the company can establish that the condition should be included in an OTC drug monograph.

Also, most manufacturers would experience a paperwork savings when applying for OTC drug monograph status instead of an NDA. For example, in most instances, the manufacturing controls information needed for submitting an NDA will not be required for a monograph submission. Ongoing recordkeeping and reporting requirements associated with periodic and annual reports would also be avoided. Based on previous estimates of the paperwork hours needed to comply with these requirements and assuming a 33 percent reduction in paperwork activities, FDA estimates that eliminating manufacturing controls information from an application would bring a one-time savings of approximately 530 hours and an annual savings of 40 hours per submission. Applying the 1995 labor rate of $29.50 per hour for an industrial engineer (Ref. 3) (with a 40 percent adjustment for benefits), these one-time savings are approximately $15,635 (530 x $29.50/hour) per submission. Likewise, using the 1995 professional and managerial labor rate of $24.60 per hour (Ref. 3) (including a 40 percent benefit rate), the ongoing savings from the elimination of periodic and annual reports would equal approximately $984 (40 x $24.60/hour) per product.

Moreover, once a condition has been included in an OTC drug monograph, other companies could achieve similar benefits, as they would be permitted to enter the marketplace without submitting an NDA or an abbreviated NDA (ANDA), hereafter referred to as an application. These companies would even avoid the costs associated with achieving the inclusion of a condition in a monograph. In addition, these companies, as well as the sponsoring companies, would be permitted to market variations of a product, such as different product concentrations or dosage forms, if allowed by the monograph, saving the cost of an application or supplement when required.

Consumers would also benefit from this rule. As conditions not previously marketed in the United States obtain OTC drug monograph status, a greater selection of OTC drug products would become available. In addition, competition from these additional products may restrain prices for the entire product class.

B. Regulatory Costs

FDA estimates that the information needed for a TEA to meet the eligibility criteria for ''material time'' and ''material extent'' would take firms approximately 480 hours to prepare. Using the 1995 professional and managerial labor rate of $24.60 per hour (Ref. 3) (including a 40 percent benefit rate), this cost amounts to approximately $12,000 (480 hours x $24.60/hour) per submission. The costs associated with requiring publication in an official compendium, where applicable, would be minimal as similar information is often prepared for publication in a foreign pharmacopeia and most companies already have such standards as part of their manufacturing quality control procedures.

Considering the potential one-time cost savings described above of $272,481 ($256,846 + $15,635) associated with prescription drug user fees and reduced recordkeeping requirements, FDA calculates a one-time net cost savings to industry of up to $260,481 ($272,481 – $12,000) per submission. Future yearly cost savings could total $19,575 ($18,591 + $984) per product and $141,966 per establishment if this were the establishment's only product. Accordingly, if FDA receives 25 to 50 TEA submissions a year, the industry would save between $8.2 million and $16.4 million in one-time costs alone. The agency notes, however, that companies would submit conditions for OTC drug monograph status only where it would be profitable for them to do so.

There are several situations, however, where the rule may result in lost sales for some future applicants. Since 1991, FDA has approved a total of six requests for the inclusion of post-1972 U.S. OTC drug conditions in a monograph. The sponsors requested permission to market these conditions before the issuance of a final monograph, and FDA granted these requests. Several other requests are currently under agency review. This proposed rule, however, would not permit interim marketing for post-1972 conditions without an application or without inclusion of the condition in a final monograph. Therefore, this rule could result in lost sales dollars for those few manufacturers who, in the absence of this rule, might have successfully petitioned FDA to market a variation of their product prior to publication in a final monograph. Likewise, other manufacturers might experience some future lost sales dollars because they also would be restricted from marketing the product or a product variation. Although the agency cannot estimate the value of these lost sales, the limited number of requests approved to date implies that very few manufacturers would be adversely affected by this interim marketing change. Moreover, because FDA expects a short period of time between a proposal to add a condition to a monograph and the final rule, any lost sales would occur over a limited timespan.

Four of the six requests approved since 1991 involved a previously unapproved concentration, dosage form, dual claim, and product combination without OTC marketing experience.

Similar conditions would not be allowed under the proposed rule without a minimum of 5 continuous years of adequate OTC marketing experience. Therefore, these manufacturers would need to either market their product under an application for 5 years in the United States or have 5 years of sufficient marketing experience abroad to qualify for inclusion in a monograph. Other manufacturers would have to wait until the condition is included in a final monograph publication before they could market the product or a product variation without an application. Due to the limited number of requests approved to date, it is likely that few manufacturers would be significantly affected by these requirements.

C. Small Business Analysis

Although the agency believes that this rule is unlikely to have a significant economic impact on a substantial number of small entities, FDA is uncertain about the extent of the future impact. Therefore, the following regulatory flexibility analysis has been prepared:

1. Description and Objective of the Proposed Rule

As stated elsewhere in this preamble, the proposed rule would make it easier to market certain OTC drug products in the United States by amending current FDA regulations to include additional criteria and procedures by which OTC conditions may become eligible for consideration in the OTC drug monograph system. The additional criteria and procedures would specify how OTC drugs initially marketed in the United States after the OTC drug review began in 1972 and OTC drugs without any U.S. marketing experience could meet the monograph eligibility requirements. Once eligibility has been determined for a particular condition, safety and effectiveness data would be evaluated.

2. Description and Estimate of the Number of Small Entities

Census data provide aggregate industry statistics on the number of manufacturers of pharmaceutical preparations, but do not distinguish between manufacturers of prescription and OTC products. According to the Small Business Administration (SBA), manufacturers of pharmaceutical preparations with 750 or fewer employees are considered small entities. The U.S. Census does not disclose data on the number of drug manufacturing firms by employment size, but between 92 and 96 percent of drug manufacturing establishments, or approximately 650 establishments, are small under this definition (Ref. 4). Although the number of firms that are small would be less than the number of establishments, FDA still concludes that the majority of pharmaceutical preparation manufacturing firms are small entities.

The agency finds that at least 400 firms manufacture U.S.-marketed OTC drug products. Using the SBA size designation, 31 percent of these firms are large, 46 percent are small, and size data are not available for the remaining 23 percent. Therefore, approximately 184 to 276 of the affected manufacturing firms may be considered small. The agency cannot project how many of these OTC drug manufacturers would submit a TEA for consideration of an additional condition in the OTC drug monograph system.

3. Description of Reporting, Recordkeeping, and Other Compliance Requirements

To demonstrate eligibility for consideration in the OTC drug monograph system, sponsors must submit data in a TEA showing that the condition has been marketed ''for a material time'' and ''to a material extent.'' Specific requirements of the TEA are discussed in section II. of this document. All companies who choose to be considered in the OTC drug monograph system must submit these data. FDA expects that all sponsoring companies employ or have ready access to individuals who possess the skills necessary for this data preparation.

4. Identification of Federal Rules That Duplicate, Overlap, or Conflict With the Proposed Rule

The agency is not aware of any relevant Federal rules which may duplicate, overlap, or conflict with the proposed rule. The agency requests any information that may show otherwise.

5. Impact on Small Entities

As described above, this rule could result in some future lost sales dollars for a few manufacturers of post-1972 OTC drug products who would not be permitted to market a product or a product variation without an application or without the inclusion of the condition in a final OTC monograph. The agency anticipates, however, that the time between a proposal to add a condition to a monograph and the final rule will generally be short, thus limiting the impact of the change in procedures concerning interim marketing. In addition, some manufacturers could be adversely affected by the 5-year material extent and material time requirements, similarly causing a loss in future sales dollars. The agency cannot quantify these impacts. However, based on the limited number of post-1972 conditions approved to date, FDA believes that few manufacturers would be significantly affected. The agency requests comment on this issue.

6. Description of Alternatives

In developing the requirements of this proposed rule, the agency considered two alternatives. Initially, FDA thought of proposing a one-step evaluation process, where sponsors would submit safety and effectiveness data concurrently with their TEA. However, the agency decided that this process would be less efficient because it would require sponsoring companies to expend resources to prepare safety and effectiveness data before the agency determines whether eligibility criteria have been met. Likewise, the agency determined that it would be an inefficient use of its resources to review safety and effectiveness data prior to making a decision on eligibility.

The agency also considered allowing manufacturers of post-1972 U.S. OTC drugs to market prior to inclusion in a final OTC drug monograph, as long as the agency had tentatively determined that the condition is GRAS/E. This approach would be consistent with the current process for pre-1972 U.S. OTC drug conditions and with the six requests for interim marketing that the agency has granted for post-1972 OTC drug conditions. However, in order to protect the American public from unnecessary risk, the agency decided that interim marketing should not be allowed under the OTC drug monograph system either for post-1972 U.S. conditions or for conditions with no previous U.S. marketing experience. This policy is believed necessary to allow for thorough public consideration of any safety and effectiveness issues that might arise before broad marketing of the condition begins under the OTC drug monograph system. Further, post-1972 U.S. OTC conditions marketed under NDA's will continue marketing in that manner until the condition is included in the OTC drug monograph system. Finally, the policy allows for the completion of compendial monograph standards for all manufacturers to use. Because FDA expects a relatively short period of time to elapse between a proposal to add a condition to a monograph and the final rule, the agency believes the public health benefits of this rule would outweigh any sales lost over this limited timespan.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

IX. Paperwork Reduction Act of 1995

This proposed rule contains collections of information which are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). ''Collection of information'' includes any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded.

Description: FDA is proposing additional criteria and procedures by which OTC conditions may become eligible for consideration in the OTC drug monograph system. The proposed criteria and procedures address how OTC drugs initially marketed in the United States after the OTC drug review began in 1972 and OTC drugs without any U.S. marketing experience could meet the statutory definition of marketing ''to a material extent'' and ''for a material time'' and become eligible. If found eligible, the condition would be evaluated for general recognition of safety and effectiveness in accord with FDA's OTC drug monograph regulations.

Current § 330.10(a)(2) sets forth the requirements for the submission of data and information that is reviewed by FDA to evaluate a drug for general recognition of safety and effectiveness. FDA receives approximately three safety and effectiveness submissions from three sponsors each year, and FDA estimates that it takes approximately 798 hours to prepare each submission.

FDA anticipates that the number of safety and effectiveness submissions would increase to 93 annually as a result of this rulemaking. (Although FDA estimates that the number of TEA's submitted annually would be 50, the agency anticipates that 30 TEA's would be approved, and that this would result in approximately 3 safety and effectiveness submissions for each approved TEA). The time required to prepare each safety and effectiveness submission would also increase as a result of two amendments to current § 330.10(a)(2) under this proposed rule.

One proposed amendment would require the revision of the ''OTC Drug Review Information'' format and content requirements in § 330.10(a)(2) by revising items IV.A.3, IV.B.3, IV.C.3, V.A.3, V.B.3, and V.C.3 to add the words ''Identify common or frequently reported side effects'' after ''documented case reports.'' This is a clarification of current requirements for submitting documented case reports and would only require sponsors to ensure that side-effects information is identified in each submission. FDA estimates that it would take sponsors approximately 1 hour to comply with this requirement.

A second proposed amendment to current § 330.10(a)(2) would require sponsors to submit an official USP–NF drug monograph for the active ingredient(s) or botanical drug substance(s), or a proposed standard for inclusion in an article to be recognized in an official USP–NF drug monograph for the active ingredient(s) or botanical drug substance(s). (This proposed requirement is also stated in proposed § 330.14(f)(1).) FDA believes that the burden associated with this requirement would also be minimal because similar information may already have been prepared for previous publication in a foreign pharmacopeia, or companies would already have these standards as part of their quality control procedures for manufacturing the product. FDA estimates that the time required for photocopying this material would be approximately 1 hour.

Thus, the time required for preparing each safety and effectiveness submission would increase by a total of 2 hours as a result of the proposed amendments to current § 330.10(a)(2), increasing the approximate hours per each submission from 798 to 800 hours.

Under proposed § 330.14(c), sponsors must submit a TEA when requesting that a condition subject to the proposed regulation be considered for inclusion in the OTC drug monograph system. Based on the data provided and explained in the ''Analysis of Impacts'' section VII above, FDA estimates that approximately 50 TEA's would be submitted to FDA annually by approximately 25 sponsors, and the time required for preparing and submitting each TEA would be approximately 480 hours.

Under proposed § 330.14(f)(2), sponsors would be required to include in each safety and effectiveness submission all serious ADE's from each country where the condition has been or is currently marketed as a prescription or OTC drug product. Sponsors would be required to provide individual ADE reports along with a detailed summary of all serious ADE's and expected or frequently reported side effects for the condition. FDA believes that the burden associated with this requirement would be minimal because individual ADE reports are already required as part of the ''documented case reports'' in the ''OTC Drug Review Information'' under current § 330.10(a)(2). FDA estimates that the time required for preparing and submitting a detailed summary of all serious ADE's and expected or frequently reported side effects would be approximately 2 hours.

Due to the anticipated number of foreign conditions seeking immediate consideration in the OTC drug monograph system, the annual reporting burden estimated in the chart below is the annual reporting for the first 3 years following publication of the final rule. FDA anticipates a reduced burden after this time period.

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
330.10(a)(2)					
Safety and Effectiveness Submission	93	1	93	800	74,400
330.14(c)					
Time and Extent Application	25	2	50	480	24,000
330.14(f)(2)					
Adverse Drug Experience Reports	90	1	90	2	180
Total					98,580

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding the information collection by January 19, 2000, to the Office of Information and Regulatory Affairs, OMB (address above).

X. References

The following references are on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Memorandum of meeting between Hisamitsu Pharmaceutical Co., Inc., and FDA, October 4, 1994, Comment No. MM9, Docket No. 78N–0301, Dockets Management Branch.

(2) United States Pharmacopeial Convention, ''Concordance of Foreign Pharmacopeial Tests and Assays,'' *Pharmacopeial Forum*, 23(3):4009–4013, 1997.

(3) U.S. Department of Labor, Bureau of Labor Statistics, ''Employment and Earnings,'' January 1996, p. 205.

(4) U.S. Department of Commerce, Economics and Statistics Administration, Bureau of the Census, ''Industry Series Drugs,'' *1992 Census of Manufactures*, Table 4, p. 28C–12.

List of Subjects in 21 CFR Part 330

Over-the-counter drugs.

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 330 be amended as follows:

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

1. The authority citation for 21 CFR part 330 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 330.10 is amended as follows:

a. In paragraph (a)(2) by adding the words ''or until the Commissioner places the panel's recommendations on public display at the office of the Dockets Management Branch'' at the end of the second sentence;

b. In paragraph (a)(2) by adding the words ''Identify expected or frequently reported side effects.'' after the words ''Documented case reports.'' in items IV.A.3, IV.B.3, IV.C.3, V.A.3, V.B.3, and V.C.3 in the outline of ''OTC Drug Review Information''; and

c. In paragraph (a)(2) by adding item VII at the end of the outline of ''OTC Drug Review Information'';

d. In paragraph (a)(5) introductory text by removing the word ''shall'' and adding in its place the word ''may'';

e. In paragraphs (a)(5)(ii) and (a)(5)(iii) by removing the word ''all'' from the first sentence;

f. In paragraphs (a)(6)(i) and (a)(9) by removing the word ''is'' and adding in its place the words ''or a specific or specific OTC drugs are'';

g. In paragraph (a)(6)(iv) by removing the word ''quintuplicate'' and by adding in its place ''triplicate'' in the fourth sentence, by removing the words ''during regular working hours'' and by adding in their place ''between the hours of 9 a.m. and 4 p.m.'' in the sixth sentence, and by adding two sentences at the end;

h. In paragraphs (a)(7)(i) and (a)(7)(ii) by revising the first and second sentences;

i. In paragraphs (a)(10)(i) and (a)(10)(iii) by adding in the first sentence the phrase ''in response to any other notice published in the **Federal Register**,'' after the phrase ''paragraph (a)(2) of this section''; and

j. In paragraph (a)(12)(i) in the fourth sentence by removing the number ''60'' and by adding in its place the number ''90'' and by removing the word ''quadruplicate'' and by adding in its place the word ''triplicate'' to read as follows:

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

(a) * * *

(2) * * *

OTC DRUG REVIEW INFORMATION

* * * * *

VII. An official United States Pharmacopeia (USP)–National Formulary (NF) drug monograph for the active ingredient(s) or botanical drug substance(s), or a proposed standard for inclusion in an article to be recognized in an official USP–NF drug monograph for the active ingredient(s) or botanical drug substance(s). Include information showing that the official or proposed compendial monograph for the active ingredient or botanical drug substance is consistent with the active ingredient or botanical drug substance used in the studies establishing safety and effectiveness and with the active ingredient or botanical drug substance marketed in the OTC product(s) to a material extent and for a material time. If differences exist, explain why.

* * * * *

(6) * * *

(iv) * * * Alternatively, the Commissioner may satisfy this requirement by placing the panel's recommendations and the data it considered on public display at the office of the Dockets Management Branch and by publishing a notice of their availability in the **Federal Register**. This notice of availability may be included as part of the tentative order in accord with paragraph (a)(7) of this section.

(7) * * *

(i) After reviewing all comments, reply comments, and any new data and information or, alternatively, after reviewing a panel's recommendations, the Commissioner shall publish in the **Federal Register** a tentative order containing a monograph establishing conditions under which a category of OTC drugs or a specific or specific OTC drugs are generally recognized as safe and effective and not misbranded. Within 90 days, any interested person may file with the Dockets Management Branch, Food and Drug Administration, written comments or written objections

specifying with particularity the omissions or additions requested. * * *

(ii) The Commissioner may also publish in the **Federal Register** a separate tentative order containing a statement of those active ingredients reviewed and proposed to be excluded from the monograph on the basis of the Commissioner's determination that they would result in a drug product not being generally recognized as safe and effective or would result in misbranding. This order may be published when no substantive comments in opposition to the panel report or new data and information were received by the Food and Drug Administration under paragraph (a)(6)(iv) of this section or when the Commissioner has evaluated and concurs with a panel's recommendation that a condition be excluded from the monograph. Within 90 days, any interested person may file with the Dockets Management Branch, Food and Drug Administration, written objections specifying with particularity the provision of the tentative order to which objection is made. * * *

* * * * *

3. Section 330.13 is amended by adding paragraph (e) to read as follows:

§ 330.13 Conditions for marketing ingredients recommended for over-the-counter (OTC) use under the OTC drug review.

* * * * *

(e) This section applies only to conditions under consideration as part of the OTC drug review initiated on May 11, 1972, and evaluated under the procedures set forth in § 330.10. Section 330.14(h) applies to the marketing of all conditions under consideration and evaluated using the criteria and procedures set forth in § 330.14.

4. Section 330.14 is added to subpart B to read as follows:

§ 330.14 Additional criteria and procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded.

(a) *Introduction.* This section sets forth additional criteria and procedures by which OTC drugs initially marketed in the United States after the OTC drug review began in 1972 and OTC drugs without any U.S. marketing experience can be considered in the OTC drug monograph system. This section also addresses conditions regulated as a cosmetic or dietary supplement in a foreign country, that would be regulated as OTC drugs in the United States. For purposes of this section, ''condition'' means an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration, marketed for a specific OTC use, except as excluded in paragraphs (b)(2) and (b)(3) of this section. For purposes of this part, ''botanical drug substance'' means a drug substance derived from one or more plants, algae, or macroscopic fungi, but does not include a highly purified or chemically modified substance derived from such a source.

(b) *Criteria.* To be considered for inclusion in the OTC drug monograph system, the condition must meet the following criteria:

(1) The condition must be marketed for OTC purchase by consumers. If the condition is marketed in another country in a class of OTC drug products that may be sold only in a pharmacy, with or without the personal involvement of a pharmacist, it must be established that this marketing restriction does not indicate safety concerns about the condition's toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary to its use.

(2) A condition is not eligible for OTC drug monograph status if marketing in the United States is limited to prescription drug use.

(3) The condition must have been marketed OTC for a minimum of 5 continuous years in the same country or countries and in sufficient quantity, as determined in paragraphs (c)(2)(ii), (c)(2)(iii), and (c)(2)(iv) of this section.

(c) *Time and extent application.* Certain information must be provided when requesting that a condition subject to this section be considered for inclusion in the OTC drug monograph system. The following information must be provided in the format of a time and extent application (TEA):

(1) Basic information about the condition that includes a description of the active ingredient(s) or botanical drug substance(s), pharmacologic class(es), intended OTC use(s), OTC strength(s) and dosage form(s), route(s) of administration, directions for use, and the applicable existing OTC drug monograph(s) under which the condition would be marketed or the request and rationale for creation of a new OTC drug monograph(s).

(i) A detailed chemical description of the active ingredient(s) that includes a full description of the drug substance, including its physical and chemical characteristics, the method of synthesis (or isolation) and purification of the drug substance, and any specifications and analytical methods necessary to ensure the identity, strength, quality, and purity of the drug substance.

(ii) For a botanical drug substance(s), a detailed description of the botanical ingredient (including proper identification of the plant, plant part(s), alga, or macroscopic fungus used; a certificate of authenticity; and information on the grower/supplier, growing conditions, harvest location and harvest time); a qualitative description (including the name, appearance, physical/chemical properties, chemical constituents, active constituent(s) (if known), and biological activity (if known)); a quantitative description of the chemical constituents, including the active constituent(s) or other chemical marker(s) (if known and measurable); the type of manufacturing process (e.g., aqueous extraction, pulverization); and information on any further processing of the botanical substance (e.g., addition of excipients or blending).

(iii) Reference to the current edition of the U.S. Pharmacopeia (USP)–National Formulary (NF) may help satisfy the requirements in this section.

(2) A list of all countries in which the condition has been marketed, including the following information for each country:

(i) How the condition has been marketed (e.g., OTC general sales direct-to-consumer; sold only in a pharmacy, with or without the personal involvement of a pharmacist; dietary supplement; or cosmetic). If the condition has been marketed as a nonprescription pharmacy-only product, establish that this marketing restriction does not indicate safety concerns about its toxicity or other potentiality for harmful effect, the method of its use, or the collateral measures necessary to its use.

(ii) The number of dosage units sold. This should include: The total number of dosage units sold, the number of units sold by package sizes (e.g., 24 tablets, 120 milliliters (mL)), and the number of doses per package based on the labeled directions for use. This information shall be presented in two formats: On a year-by-year basis, and cumulative totals. The agency will maintain the year-to-year data as confidential, unless the sponsor waives this confidentiality. The agency will make the cumulative totals public if the condition is found eligible for consideration in the OTC drug monograph system.

(iii) A description of the marketing exposure (e.g., race, gender, ethnicity, and other pertinent factors) to ensure that the condition's use(s) can be reasonably extrapolated to the U.S.

population. If desired, sponsors may use the categories and definitions in The Office of Management and Budget's **Federal Register** notice, titled ''Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity,'' which identifies the following racial/ethnic groups: American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, and White (62 FR 58781, October 30, 1997). Explain any cultural or geographical differences in the way the condition is used in the foreign country and would be used in the United States. The information in this paragraph need not be provided for OTC drugs that have been marketed for more than 5 years in the United States under a new drug application.

(iv) The use pattern of the condition (i.e., how often it is to be used (according to the label) and for how long). If the use pattern varies in different countries based on the condition's packaging and labeling, or changes in use pattern have occurred over time, describe the use pattern for each country and explain why there are differences or changes.

(v) A description of the country's system for identifying adverse drug experiences, especially those found in OTC marketing experience, including method of collection if applicable.

(3) A statement of how long the condition has been marketed in each country, accompanied by all labeling used during the marketing period, specifying the time period that each labeling was used. All labeling that is not in English must be translated to English in accord with § 10.20(c)(2) of this chapter. The information in this paragraph need not be provided for OTC drugs that have been marketed for more than 5 years in the United States under a new drug application.

(4) A list of all countries where the condition is marketed only as a prescription drug and the reasons why its marketing is restricted to prescription in these countries.

(5) A list of all countries in which the condition has been withdrawn from marketing or in which an application for OTC marketing approval has been denied. Include the reasons for such withdrawal or application denial.

(6) The information requested in paragraphs (c)(2), (c)(2)(i) through (c)(2)(iv), and (c)(3) of this section must be provided in a table format. The labeling required by paragraph (c)(3) of this section must be attached to the table with identification of each time period that it was used.

(d) *Submission of information; confidentiality.* The sponsor must submit three copies of the TEA to the Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852. The Food and Drug Administration will handle the TEA as confidential until such time as a decision is made on the eligibility of the condition for consideration in the OTC drug monograph system. If the condition is found eligible, the TEA will be placed on public display in the Dockets Management Branch after deletion of information deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). Sponsors must identify information that is considered confidential under these provisions. If the condition is not found eligible, the TEA will not be placed on public display, but a letter from the agency to the sponsor stating why the condition was not found acceptable will be placed on public display in the Dockets Management Branch.

(e) *Notice of eligibility.* If the condition is found eligible, the agency will publish a notice of eligibility in the **Federal Register** and provide the sponsor and other interested parties an opportunity to submit data to demonstrate safety and effectiveness. When the notice of eligibility is published, the agency will place the TEA on public display in the Dockets Management Branch.

(f) *Request for data and views.* The notice of eligibility shall request interested persons to submit published and unpublished data to demonstrate the safety and effectiveness of the condition for its intended OTC use(s). These data shall be submitted to a docket established in the Dockets Management Branch and shall be publicly available for viewing at that office, except data deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). Data considered confidential under these provisions must be clearly identified. Any proposed compendial standards for the condition shall not be considered confidential. The safety and effectiveness submissions shall include the following:

(1) All data and information listed in § 330.10(a)(2) under the outline ''OTC Drug Review Information'' items III through VII.

(2) All serious adverse drug experiences as defined in §§ 310.305 and 314.80 of this chapter, from each country where the condition has been or is currently marketed as a prescription drug or as an OTC drug or product. Provide individual adverse drug experience reports (FDA form 3500A or equivalent) along with a summary of all serious adverse drug experiences, and expected or frequently reported side effects for the condition. Individual reports that are not in English must be translated to English in accord with § 10.20(c)(2) of this chapter.

(g) *Administrative procedures.* The agency may use an advisory review panel to evaluate the safety and effectiveness data in accord with the provisions of § 330.10(a)(3). Alternatively, the agency may evaluate the data in conjunction with the advisory review panel or on its own without using an advisory review panel. The agency will use the safety, effectiveness, and labeling standards in § 330.10(a)(4)(i) through (a)(4)(vi) in evaluating the data.

(1) If the agency uses an advisory review panel to evaluate the data, the panel may submit its recommendations in its official minutes of meeting(s) or by a report under the provisions of § 330.10(a)(5).

(2) The agency may act on an advisory review panel's recommendations using the procedures in § 330.10(a)(2) and (a)(6) through (a)(10).

(3) If the condition is initially determined to be generally recognized as safe and effective for OTC use in the United States, the agency will propose to include it in an appropriate OTC drug monograph(s), either by amending an existing monograph(s) or establishing a new monograph(s), if necessary.

(4) If the condition is initially determined not to be generally recognized as safe and effective for OTC use in the United States, the agency will inform the sponsor and other interested parties who have submitted data of its determination by letter, a copy of which will be placed on public display in the docket established in the Dockets Management Branch. The agency will publish a notice of proposed rulemaking to include the condition in § 310.502 of this chapter.

(5) Interested parties will have an opportunity to submit comments and new data. The agency will subsequently publish a final rule (or reproposal if necessary) in the **Federal Register**.

(h) *Marketing.* A condition submitted under this section for consideration in the OTC drug monograph system may be marketed in accordance with an applicable final OTC drug monograph(s) only after the agency determines that the condition is generally recognized as safe and effective and includes it in the appropriate OTC drug final monograph(s) and the condition complies with paragraph (i) of this section.

(i) *Compendial monograph.* Any active ingredient or botanical drug

substance included in a final OTC drug monograph must be recognized in an official USP–NF drug monograph that sets forth its standards of identity, strength, quality, and purity. Sponsors must include an official or proposed compendial monograph as part of the safety and effectiveness data submission under item VII of the OTC Drug Review Information in § 330.10(a)(2).

Dated: September 10, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 99–32428 Filed 12–17–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[REG–106012–98]

RIN 1545–AW17

Definition of Contribution in Aid of Construction Under Section 118(c)

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Notice of proposed rulemaking and notice of public hearing.

SUMMARY: This document contains proposed regulations concerning the definition of a contribution in aid of construction under section 118(c) and the adjusted basis of any property acquired with a contribution in aid of construction. The proposed regulations affect a regulated public utility that provides water or sewerage services because a qualifying contribution in aid of construction is treated as a contribution to the capital of the utility and excluded from gross income. This document also provides notice of a public hearing on these proposed regulations.

DATES: Written and electronic comments must be received by March 22, 2000.

Outlines of topics to be discussed at the public hearing scheduled for April 27, 2000, must be received by April 6, 2000.

ADDRESSES: Send submissions to: CC:DOM:CORP:R (REG–106012–98), room 5226, Internal Revenue Service, POB 7604, Ben Franklin Station, Washington, DC 20044. Submissions may be hand delivered Monday through Friday between the hours of 8 a.m. and 5 p.m. to: CC:DOM:CORP:R (REG–106012–98), Courier's Desk, Internal Revenue Service, 1111 Constitution Avenue, NW., Washington, DC. Alternatively, taxpayers may submit comments electronically via the Internet by selecting the ''Tax Regs'' option on the IRS Home Page, or by submitting comments directly to the IRS Internet site at http://www.irs.ustreas.gov/tax__regs/regslist.html. The public hearing will be held in room 2615, Internal Revenue Building, 1111 Constitution Avenue, NW., Washington, DC.

FOR FURTHER INFORMATION CONTACT: Concerning the regulations, Paul Handleman, (202) 622–3040; concerning submissions, the hearing, and/or to be placed on the building access list to attend the hearing, LaNita Van Dyke, (202) 622–7180 (not toll-free numbers).

SUPPLEMENTARY INFORMATION:

Paperwork Reduction Act

The collection of information contained in this notice of proposed rulemaking has been submitted to the Office of Management and Budget for review in accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)). Comments on the collection of information should be sent to the Office of Management and Budget, Attn: Desk Officer for the Department of the Treasury, Office of Information and Regulatory Affairs, Washington, DC 20503, with copies to the Internal Revenue Service, Attn: IRS Reports Clearance Officer, OP:FS:FP, Washington, DC 20224.

Comments on the collection of information should be received by February 18, 2000.

Comments are specifically requested concerning:

Whether the proposed collection of information is necessary for the proper performance of the functions of the IRS, including whether the information will have practical utility;

The accuracy of the estimated burden associated with the proposed collection of information (see below);

How the quality, utility, and clarity of the information to be collected may be enhanced;

How the burden of complying with the proposed collection of information may be minimized, including through the application of automated collection techniques or other forms of information technology; and

Estimates of capital or start-up costs and costs of operation, maintenance, and purchase of services to provide information.

The requirement for the collection of information in this notice of proposed rulemaking is in § 1.118–2(e). The information is required by the IRS to establish that a taxpayer has notified the IRS of amounts to be treated as a contribution to capital under section 118(c). This information will be used to determine when the statutory period for the assessment of any deficiency attributable to any contribution to capital under section 118(c) expires. The collection of information is mandatory. The likely respondents are businesses and other for-profit organizations.

Estimated total annual reporting burden: 100 hours.

The estimated annual burden per respondent varies from .5 hours to 5 hours, depending on individual circumstances, with an estimated average of 1 hour.

Estimated number of respondents: 100.

Estimated annual frequency of responses: annually.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the collection of information displays a valid control number assigned by the Office of Management and Budget.

Books or records relating to a collection of information must be retained as long as their contents may become material in the administration of any internal revenue law. Generally, tax returns and tax return information are confidential, as required by 26 U.S.C. 6103.

Background

This document contains proposed amendments to the Income Tax Regulations (26 CFR part 1) to provide regulations under section 118(c) of the Internal Revenue Code of 1986. Section 118(c) was added to the Code by section 1613(a)(1)(B) of the Small Business Job Protection Act of 1996 (SBJPA of 1996), 1996–3 C.B. 155, 248–250. Under section 1613(a)(3) of the SBJPA of 1996, the amendments made by section 1613(a) apply to amounts received after June 12, 1996.

Explanation of Provisions

Contribution to Capital

Section 118(a) generally provides that, in the case of a corporation, gross income does not include any contribution to the capital of the taxpayer. Under section 118(b), a contribution in aid of construction generally is not a contribution to the capital of the taxpayer and is not excluded from gross income under section 118(a). However, for amounts received after June 12, 1996, section 118(c) provides an exception to this rule.

Under section 118(c)(1), the term ''contribution to the capital of the