(2) An active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by the panel in category II (conditions subject to § 330.10(a)(6)(ii)), may be marketed only after:

(i) The Center for Drug Evaluation and Research or the Commissioner tentatively determines that the ingredient is generally recognized as safe and effective, and the Commissioner states by notice in the FEDERAL REGISTER (separately or as part of another document) that marketing under specified conditions will be permitted;

(ii) The ingredient is determined by the Commissioner to be generally recognized as safe and effective and is included in the appropriate published OTC drug final monograph; or

(iii) A new drug application for the product has been approved.

(d) An OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by the panel in category III (conditions subject to § 330.10(a)(6)(iii)), may be marketed only after:

(i) The Center for Drug Evaluation and Research or the Commissioner tentatively determines that the ingredient is generally recognized as safe and effective, and the Commissioner states by notice in the FEDERAL REGISTER (separately or as part of another document) that marketing under specified conditions will be permitted;

(ii) The ingredient is determined by the Commissioner to be generally recognized as safe and effective and is included in the appropriate published OTC drug final monograph; or

(iii) A new drug application for the product has been approved.

(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.

[41 FR 32582, Aug. 4, 1976, as amended at 47 FR 17739, Apr. 23, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11581, Mar. 29, 1990; 67 FR 3074, Jan. 23, 2002]

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

This section sets forth additional criteria and procedures by which over-the-counter (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. Section 330.15 sets forth timelines for FDA review and action.

(a) *Definitions.* The definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act and the following definitions of terms apply to this section and to § 330.15.

(1) *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.

(2) *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 paragraph (b)(2) of this section.

(3) *Date of filing* means the date of the notice from FDA stating that FDA has made a threshold determination that the safety and effectiveness data submission is sufficiently complete to permit a substantive review; or, if the submission is filed over protest in accordance with paragraph (j)(3) of this section, the date of filing is the date of the notice from FDA stating that FDA has filed the submission over protest

(this date will be no later than 30 days after the request that FDA file the submission over protest).

(4) *Feedback letter* means a letter issued by the agency in accordance with paragraph (g)(4) of this section that informs the sponsor and other interested persons who have submitted data under paragraph (f) of this section that a condition is initially determined not to be generally recognized as safe and effective (GRASE).

(5) *Safety and effectiveness data submission* means a data package submitted by a sponsor or other interested person that includes safety and effectiveness data and information under paragraph (f) of this section and that is represented by the submitter as being a complete submission.

(6) *Sponsor* means the person that submitted a time and extent application (TEA) under paragraph (c) of this section.

(7) *Time and extent application (TEA)* means a submission by a sponsor under paragraph (c) of this section, which will be evaluated by the agency to determine eligibility of a condition for consideration in the OTC drug monograph system.

(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) The condition must have been marketed OTC for a minimum of 5 continuous years in the same country and in sufficient quantity, as determined in paragraphs (c)(2)(ii), (c)(2)(iii), and (c)(2)(iv) of this section. Depending on the condition's extent of marketing in only one country with 5 continuous years of marketing, marketing in more than one country may be necessary.

(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) or foreign compendiums may help satisfy the requirements in this section.

(2) A list of all countries in which the condition has been marketed. Include

the following information for each country. (For a condition that has been marketed OTC in 5 or more countries with a minimum of 5 continuous years of marketing in at least one country, the sponsor may submit information in accordance with paragraph (c)(4) of this section):

(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 cumulative total number of dosage units (e.g., tablets, capsules, ounces) sold for each dosage form of the condition. Manufacturers or suppliers of OTC active ingredients may provide dosage unit information as the total weight of active ingredient sold. List the various package sizes for each dosage form in which the condition is marketed OTC. Provide an estimate of the minimum number of potential consumer exposures to the condition using one of the following calculations:

(A) Divide the total number of dosage units sold by the number of dosage units in the largest package size marketed, or

(B) Divide the total weight of the active ingredient sold by the total weight of the active ingredient in the largest package size marketed.

(iii) A description of the population demographics (percentage of various racial/ethnic groups) and the source(s) from which this information has been compiled, to ensure that the condition's use(s) can be reasonably extrapolated to the U.S. population.

(iv) If the use pattern (*i.e.*, how often it is to be used (according to the label) and for how long) varies between countries based on the condition's packaging and labeling, or changes in use pattern have occurred over time in one or more countries, 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 and how long the current product labeling has been in use, accompanied by a copy of the current product labeling. All labeling that is not in English must be translated to English in accordance with §10.20(c)(2) of this chapter. State whether the current product labeling has or has not been authorized, accepted, or approved by a regulatory body in each country where the condition is marketed.

(4) For a condition that has been marketed OTC in five or more countries with a minimum of 5 continuous years of marketing in at least one country, the sponsor may select at least five of these countries from which to submit information in accord with paragraphs (c)(2)(i) through (c)(2)(iv) of this section. Selected countries must include the country with a minimum of 5 continuous years of OTC marketing, countries that have the longest duration of marketing, and countries having the most support for extent of marketing, *i.e.*, a large volume of sales with cultural diversity among users of the product. If the condition meets these criteria in countries listed in section 802(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act, some of these countries should be included among the five selected. Sponsors should provide information from more than five countries if they believe that it is needed to support eligibility. Sponsors should explain the basis for the countries selected in the TEA.

(5) 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.

(6) 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.

(7) 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.

(8) For OTC drugs that have been marketed for more than 5 years in the United States under a new drug application, the information requested in paragraphs (c)(2)(i), (c)(2)(iii), (c)(2)(v), (c)(3), and (c)(5) of this section need not be provided.

(d) *Submission of information*; *confidentiality*. The sponsor must submit three copies of the TEA to the Central Document Room, 5630 Fishers Lane, rm. 1061, 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 Division of Dockets Management 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 statutory 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 Division of Dockets Management.

(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 Division of Dockets Management.

(f) *Safety and effectiveness data submission*. The notice of eligibility will request a safety and effectiveness data submission that includes published and unpublished data to demonstrate the safety and effectiveness of the condition for its intended OTC use(s), as well as the submission of any other relevant data and views. These data will be submitted to a docket established in the Division of Dockets Management and will 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 will not be considered confidential. The safety and effectiveness data submission must be sufficiently complete to be filed by the agency under paragraph (j)(2) of this section. Safety and effectiveness data and other information submitted under this paragraph are subject to the requirements in § 330.10(c), (e), and (f). The safety and effectiveness data submission must 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 accordance 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 330.10(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 GRASE for OTC use in the United States, the agency will inform the sponsor and other interested persons who have submitted data of its determination by feedback letter, a copy of which will be placed on public display in the docket established in the Division of Dockets Management. 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. When an OTC drug monograph has not been finalized and finalization is not imminent, after the agency has evaluated the comments to a proposed rule to include a new condition in a tentative final monograph as generally recognized as safe and effective and the agency has not changed its position as a result of the comments, and the condition complies with paragraph (i) of this section, the agency may publish a notice of enforcement policy that allows marketing to begin pending completion of the final monograph subject to the risk that the agency may, prior to or in the final monograph, adopt a different position that could require relabeling, recall, or other regulatory action.

(i) *Compendial monograph.* Any active ingredient or botanical drug substance included in a final OTC drug monograph or the subject of an enforcement notice described in paragraph (h) of this section 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 listed in § 330.10(a)(2) under item VII of the outline entitled ''OTC DRUG REVIEW INFORMATION.''

(j) *Filing determination.* (1) After FDA receives a safety and effectiveness data submission, the agency will determine whether the submission may be filed. The filing of a submission means that FDA has made a threshold determination that the submission is sufficiently complete to permit a substantive review.

(2) If FDA finds that none of the reasons in paragraph (j)(4) of this section for refusing to file the safety and effectiveness data submission apply, the agency will file the submission and notify the submitter in writing. FDA will post a copy of the notice to the docket. The date of filing begins the FDA timelines described in § 330.15(c)(3) and (4). Data submitted after the date of filing will be considered before the issuance of a notice of proposed rulemaking if there is adequate time for review; otherwise, the data will be considered as comments to the proposed rule after issuance of a notice of proposed rulemaking.

(3) If FDA refuses to file the safety and effectiveness data submission, the agency will notify the submitter in writing and state the reason(s) under paragraph (j)(4) of this section for the refusal. The submitter may request in writing, within 30 days of the date of the agency's notification, a meeting with the agency about whether the agency should file the submission, and FDA will convene the meeting within 30 days of the request. If, within 120 days after the meeting, the submitter requests that FDA file the submission (with or without correcting the deficiencies), the agency will file the safety and effectiveness data submission over protest under paragraph (j)(2) of this section, notify the submitter in writing and post a copy to the docket, and review the submission as filed. The

submitter must have a meeting before requesting that FDA file the submission over protest but need not resubmit a copy of a safety and effectiveness data submission that is filed over protest. A safety and effectiveness data submission and the corresponding TEA-eligible condition are both not deemed under consideration if FDA refuses to file the safety and effectiveness data submission, and it is not filed over protest; the condition remains eligible for consideration and the sponsor or any interested person can pursue consideration of the condition in the future by submitting a new safety and effectiveness data submission.

(4) FDA may refuse to file a safety and effectiveness data submission if any of the following applies:

(i) The submission is incomplete because it does not contain information required under paragraph (f) of this section. If the submission does not contain required information because such information or data are not relevant to the condition, the submission must clearly identify and provide an explanation for the omission.

(ii) The submission is not organized or formatted in a manner to enable the agency to readily determine whether it is sufficiently complete to permit a substantive review.

(iii) The submission does not contain a signed statement that the submission represents a complete safety and effectiveness data submission and that the submission includes all the safety and effectiveness data and information available to the submitter at the time of the submission, whether positive or negative.

(iv) The submission does not contain an analysis and summary of the data and other supporting information, organized by clinical or nonclinical area, such as clinical efficacy data, clinical safety data, clinical pharmacology, adverse event reports, animal toxicology, chemistry data, and compendial status.

(v) The submission does not contain a supporting document summarizing the strategy used for literature searches, including search terms, sources, dates accessed, and years reviewed.

(vi) The submission does not contain a reference list of supporting information, such as published literature, unpublished information, abstracts and case reports, and a copy of the supporting information.

(vii) The submission includes data or information relevant for making a GRASE determination marked as confidential without a statement that the information may be released to the public.

(viii) The submission does not contain a complete environmental assessment under § 25.40 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.30 or § 25.31 of this chapter.

(ix) The submission does not contain a statement for each nonclinical laboratory study that the study was conducted in compliance with the requirements set forth in part 58 of this chapter, or, if it was not conducted in compliance with part 58 of this chapter, a brief statement of the reason for the noncompliance.

(x) The submission does not contain a statement for each clinical investigation involving human subjects that the investigation was conducted in compliance with the institutional review board regulations in part 56 of this chapter, or was not subject to those regulations, and that the investigation was conducted in compliance with the informed consent regulations in part 50 of this chapter.

(xi) The submission does not include financial certification or disclosure statements, or both, as required by part 54 of this chapter, accompanying any clinical data submitted.

(k) *Withdrawal of consideration.* (1) Notwithstanding paragraph (g) of this section, FDA may withdraw consideration of a TEA submission or a safety and effectiveness data submission if:

(i) The person that submitted the submission requests that its submission be withdrawn from consideration; or

(ii) FDA deems the submission to be withdrawn from consideration due to the submitter's failure to respond to communications from FDA.

(2) Before FDA deems a submission withdrawn under paragraph (k)(1)(ii) of this section, FDA will notify the person that submitted the submission. If,

within 90 days from the date of the notice from FDA, the submitter requests that FDA not withdraw consideration of the submission, FDA will not deem the submission to be withdrawn.

(3) If FDA withdraws consideration of a submission under paragraph (k)(1) of this section, FDA will post a notice of withdrawal to the docket, except in the case of a TEA submission that is withdrawn from consideration before issuance of a notice of eligibility, in which case, the notice of withdrawal will only be provided to the sponsor. Information that has been posted to the public docket for the condition at the time of the withdrawal (such as a notice of eligibility or a safety and effectiveness data submission that has been accepted for filing and posted to the docket) will remain in the public docket. If the condition has been found eligible through issuance of a notice of eligibility, the condition remains eligible for consideration and the sponsor or any interested person can pursue consideration of the condition in the future by submitting a new safety and effectiveness data submission.

(4) If FDA withdraws consideration of a submission under paragraph (k)(1) of this section, the timelines under § 330.15(c) will no longer apply as of the date of withdrawal, and the submission will not be included in the metrics under § 330.15(b).

[67 FR 3074, Jan. 23, 2002, as amended at 81 FR 84475, Nov. 23, 2016]

§ 330.15 Timelines for FDA review and action on time and extent applications and safety and effectiveness data submissions.

(a) *Applicability*. This section applies to the review of a condition in a time and extent application (TEA) submitted under § 330.14 for consideration in the over-the-counter (OTC) drug monograph system. This section does not apply to:

(1) A sunscreen active ingredient or combination of sunscreen active ingredients, and other conditions for such ingredients; or

(2) A non-sunscreen active ingredient or combination of non-sunscreen active ingredients, and other conditions for such ingredients submitted in a TEA under § 330.14 before November 27, 2014, subject to section 586F(a)(1)(C) of the Federal Food, Drug, and Cosmetic Act.

(b) *Metrics*. FDA will maintain and update annually, a publicly available posting of metrics for the review of TEAs and safety and effectiveness data submissions that are subject to the timelines in this section. The posting will contain the following information for tracking the extent to which the timelines set forth in paragraph (c) of this section were met during the previous calendar year.

(1) Number and percent of eligibility notices or ineligibility letters issued within 180 days of submission of a TEA;

(2) Number and percent of filing determinations issued within 90 days of submission of a safety and effectiveness data submission;

(3) If applicable, number and percent of feedback letters issued within 730 days from the date of filing;

(4) Number and percent of notices for proposed rulemaking issued within 1,095 days from the date of filing;

(5) Number and percent of final rules issued within 912 days of closing of the docket of the proposed rulemaking; and

(6) Total number of TEAs submitted under § 330.14.

(c) *Timelines for FDA review and action*. FDA will review and take an action within the following timelines:

(1) Within 180 days of submission of a TEA under § 330.14(c), FDA will issue a notice of eligibility or post to the docket a letter of ineligibility, in accordance with § 330.14(d) and (e).

(2) Within 90 days of submission of a safety and effectiveness data submission, in accordance with § 330.14(j), FDA will issue a filing determination. The date of filing begins the FDA timelines in paragraphs (c)(3) and (4) of this section.

(3) Within 730 days from the date of filing, if the condition is initially determined not to be GRASE for OTC use in the United States, FDA will inform the sponsor and other interested persons who have submitted data of its determination by feedback letter in accordance with § 330.14(g)(4).

(4) Within 1,095 days from the date of filing of a safety and effectiveness data submission, FDA will issue a notice of proposed rulemaking to either: