(ii) Patient age at the time of adverse drug experience, or date of birth;
(iii) Patient gender; and
(iv) Patient weight.
(2) *Adverse event.*
(i) Outcome attributed to adverse drug event;
(ii) Date of adverse drug event;
(iii) Date of ICSR submission;
(iv) Description of adverse drug event (including a concise medical narrative);
(v) Adverse drug event term(s);
(vi) Description of relevant tests, including dates and laboratory data; and
(vii) Other relevant patient history, including preexisting medical conditions.
(3) *Suspect medical product(s).*
(i) Name;
(ii) Dose, frequency, and route of administration used;
(iii) Therapy dates;
(iv) Diagnosis for use (indication);
(v) Whether the product is a combination product as defined in §3.2(e) of this chapter;
(vi) Whether the product is a prescription or nonprescription product;
(vii) Whether adverse drug event abated after drug use stopped or dose reduced;
(viii) Whether adverse drug event reappeared after reintroduction of drug;
(ix) Lot number;
(x) Expiration date;
(xi) National Drug Code (NDC) number; and
(xii) Concomitant medical products and therapy dates.
(4) *Initial reporter information.*
(i) Name, address, and telephone number;
(ii) Whether the initial reporter is a health care professional; and
(iii) Occupation, if a health care professional.
(5) *Responsible person (as defined in section 760(b) of the FD&C Act) information.*
(i) Name and contact office address;
(ii) Telephone number;
(iii) Report source, such as spontaneous;
(iv) Date the report was received by responsible person;
(v) Whether the ICSR is a 15-day report;
(vi) Whether the ICSR is an initial report or followup report; and
(vii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(c) *Electronic format for submissions.* (1) Each report required to be submitted to FDA under section 760 of the FD&C Act, accompanied by a copy of the label on or within the retail package of the drug and any other documentation (as ICSR attachments), must be in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation, and organization of files).

(2) The responsible person may request, in writing, a temporary waiver of the requirements in paragraph (c)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (c)(1) of this section.

(d) *Patient privacy.* The responsible person should not include in reports under this section the names and addresses of individual patients; instead, the responsible person should assign a unique code for identification of the patient. The responsible person should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug event reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

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

Subpart A—General Provisions

Sec.

Subpart B—Administrative Procedures

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360fff–6, 371.

SOURCE: 39 FR 11741, Mar. 29, 1974, unless otherwise noted.

EDITORIAL NOTE: Nomenclature changes to part 330 appear at 69 FR 13717, Mar. 24, 2004.

Subpart A—General Provisions

§ 330.1 General conditions for general recognition as safe, effective and not misbranded.

An over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph. Any product which fails to conform to each of the conditions contained in this part and in an applicable monograph is liable to regulatory action.

(a) The product is manufactured in compliance with current good manufacturing practices, as established by parts 210 and 211 of this chapter.

(b) The establishment(s) in which the drug product is manufactured is registered, and the drug product is listed, in compliance with part 207 of this chapter. It is requested but not required that the number assigned to the product pursuant to part 207 of this chapter appear on all drug labels and in all drug labeling. If this number is used, it shall be placed in the manner set forth in part 207 of this chapter.

(c)(1) The product is labeled in compliance with chapter V of the Federal Food, Drug, and Cosmetic Act (the act) and subchapter C *et seq.* of this chapter, including the format and content requirements in § 201.66 of this chapter. An OTC drug product that is not in compliance with chapter V and subchapter C, including § 201.66 of this chapter, is subject to regulatory action. For purposes of § 201.61(b) of this chapter, the statement of identity of the product shall be the term or phrase used in the applicable OTC drug monograph established in this part.

(2) The ''Uses'' section of the label and labeling of the product shall contain the labeling describing the ''Indications'' that have been established in an applicable OTC drug monograph or alternative truthful and nonmisleading statements describing only those indications for use that have been established in an applicable monograph, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act. Any other labeling under this subchapter and subchapter C *et seq.* of this chapter shall be stated in the exact language where exact language has been established and identified by quotation marks in an applicable OTC drug monograph or by regulation (e.g., § 201.63 of this chapter), except as provided in paragraphs (i) and (j) of this section.

(d) The advertising for the product prescribes, recommends, or suggests its use only under the conditions stated in the labeling.

(e) The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 721 of the act and subchapter A of this chapter.

(f) The product container and container components meet the requirements of § 211.94 of this chapter.

(g) The labeling for all drugs contains the general warning: ''Keep out of reach of children.'' [highlighted in bold

type]. The labeling of drugs shall also state as follows: For drugs used by oral administration, ''In case of overdose, get medical help or contact a Poison Control Center right away''; for drugs used topically, rectally, or vaginally and not intended for oral ingestion, ''If swallowed, get medical help or contact a Poison Control Center right away''; and for drugs used topically and intended for oral use, ''If more than used for'' (insert intended use, e.g., pain) ''is accidentally swallowed, get medical help or contact a Poison Control Center right away.'' The Food and Drug Administration will grant an exemption from these general warnings where appropriate upon petition, which shall be maintained in a permanent file for public review by the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(h) Where no maximum daily dosage limit for an active ingredient is established in this part, it is used in a product at a level that does not exceed the amount reasonably required to achieve its intended effect.

(i) The following terms may be used interchangeably in the labeling of OTC drug products, provided such use does not alter the meaning of the labeling that has been established and identified in an applicable monograph or by regulation. The following terms shall not be used to change in any way the title, headings, and subheadings required under § 201.66(c)(1) through (c)(9) of this chapter:

(1) ''Abdominal'' or ''stomach'' (in context only).

(2) ''Administer'' or ''give''.

(3) ''Aggravate(s)'' or ''make(s) worse''.

(4) ''Application of this product'' or ''applying''.

(5) ''Are uncertain'' or ''do not know''.

(6) ''Ask'' or ''consult'' or ''contact''.

(7) ''Asking'' or ''consulting''.

(8) ''Assistance'' or ''help'' or ''aid''.

(9) ''Associated with'' or ''due to'' or ''caused by''.

(10) ''Avoid contact with eyes'' or ''do not get into eyes''.

(11) ''Avoid inhaling'' or ''do not inhale''.

(12) ''Before a doctor is consulted'' or ''without first consulting your doctor'' or ''consult your doctor before''.

(13) ''Beverages'' or ''drinks''.

(14) ''Clean'' or ''cleanse''.

(15) ''Consulting'' or ''advising''.

(16) ''Continue(s)'' or ''persist(s)'' or ''is persistent'' or ''do(es) not go away'' or ''last(s)''.

(17) ''Daily'' or ''every day''.

(18) ''Develop(s)'' or ''begin(s)'' or ''occur(s)''.

(19) ''Difficulty'' or ''trouble''.

(20) ''Difficulty in urination'' or ''trouble urinating''.

(21) ''Discard'' or ''throw away''.

(22) ''Discontinue'' or ''stop'' or ''quit''.

(23) ''Doctor'' or ''physician''.

(24) ''Drowsiness'' or ''the drowsiness effect''.

(25) ''Drowsiness may occur'' or ''you may get drowsy''.

(26) ''Enlargement of the'' or ''an enlarged''.

(27) ''Especially in children'' or especially children''.

(28) ''Exceed'' or ''use more than'' or ''go beyond''.

(29) ''Exceed recommended dosage'' or ''use more than directed''.

(30) ''Excessive'' or ''too much''.

(31) ''Excitability may occur'' or ''you may get excited''.

(32) ''Experience'' or ''feel''.

(33) ''For relief of'' or ''relieves''.

(34) ''For temporary reduction of'' or ''temporarily reduces''.

(35) ''For the temporary relief of'' or ''temporarily relieves''.

(36) ''For the treatment of'' or ''treats''.

(37) ''Frequently'' or ''often''.

(38) ''Give to'' or ''use in''.

(39) ''Immediately'' or ''right away'' or ''directly''.

(40) ''Immediately'' or ''as soon as''.

(41) ''Immediately following'' or ''right after''.

(42) ''Improve(s)'' or ''get(s) better'' or ''make(s) better''.

(43) ''Increased'' or ''more''.

(44) ''Increase your risk of'' or ''cause''.

(45) ''Indication(s)'' or ''Use(s)''.

(46) ''Inhalation'' or ''puff''.

(47) ''In persons who'' or ''if you'' or ''if the child''.

(48) ''Instill'' or ''put''.

(49) ''Is (are) accompanied by'' or ''you also have'' (in context only) or ''(optional: that) occur(s) with''.
(50) ''Longer'' or ''more''.
(51) ''Lung'' or ''pulmonary''.
(52) ''Medication(s)'' or ''medicine(s)'' or ''drug(s)''.
(53) ''Nervousness, dizziness, or sleeplessness occurs'' or ''you get nervous, dizzy, or sleepless''.
(54) ''Not to exceed'' or ''do not exceed'' or ''not more than''.
(55) ''Obtain(s)'' or ''get(s)''.
(56) ''Passages'' or ''passageways'' or ''tubes''.
(57) ''Perforation of'' or ''hole in''.
(58) ''Persistent'' or ''that does not go away'' or ''that continues'' or ''that lasts''.
(59) ''Per day'' or ''daily''.
(60) ''Presently'' or ''now''.
(61) ''Produce(s)'' or ''cause(s)''.
(62) ''Prompt(ly)'' or ''quick(ly)'' or ''right away''.
(63) ''Reduce'' or ''minimize''.
(64) ''Referred to as'' or ''of''.
(65) ''Sensation'' or ''feeling''.
(66) ''Solution'' or ''liquid''.
(67) ''Specifically'' or ''definitely''.
(68) ''Take'' or ''use'' or ''give''.
(69) ''Tend(s) to recur'' or ''reoccur(s)'' or ''return(s)'' or ''come(s) back''.
(70) ''To avoid contamination'' or ''avoid contamination'' or ''do not contaminate''.
(71) ''To help'' or ''helps''.
(72) ''Unless directed by a doctor'' or ''except under the advice of a doctor'' or ''unless told to do so by a doctor''.
(73) ''Use caution'' or ''be careful''.
(74) ''Usually'' or ''generally'' (in context only).
(75) ''You'' (''Your'') or ''the child'' (''the child's'').
(76) ''You also have'' or ''occurs with''.
(77) ''When practical'' or ''if possible''.
(78) ''Whether'' or ''if''.
(79) ''Worsen(s)'' or ''get(s) worse'' or ''make(s) worse''.

(j) The following connecting terms may be deleted from the labeling of OTC drug products, provided such deletion does not alter the meaning of the labeling that has been established and identified in an applicable monograph or by regulation. The following terms shall not be used to change in any way the specific title, headings, and subheadings required under §201.66(c)(1) through (c)(9) of this chapter:
(1) ''And''.
(2) ''As may occur with''.
(3) ''Associated'' or ''to be associated''.
(4) ''Consult a doctor''.
(5) ''Discontinue use''.
(6) ''Drug Interaction Precaution''.
(7) ''Due to''.
(8) ''Except under the advice and supervision of a physician''.
(9) ''If this occurs''.
(10) ''In case of''.
(11) ''Notice''.
(12) ''Or''.
(13) ''Occurring with''.
(14) ''Or as directed by a doctor''.
(15) ''Such as''.
(16) ''Such as occurs with''.
(17) ''Tends to''.
(18) ''This product''.
(19) ''Unless directed by a doctor''.
(20) ''While taking this product'' or ''before taking this product''.
(21) ''Within''.

[39 FR 11741, Mar. 29, 1974, as amended at 40 FR 11718, Mar. 13, 1975; 40 FR 13496, Mar. 27, 1975; 42 FR 15674, Mar. 22, 1977; 46 FR 8459, Jan. 27, 1981; 50 FR 8996, Mar. 6, 1985; 51 FR 16266, May 1, 1986; 55 FR 11581, Mar. 29, 1990; 59 FR 4000, Jan. 28, 1994; 59 FR 14365, Mar. 28, 1994; 64 FR 13294, Mar. 17, 1999; 68 FR 24879, May 9, 2003; 88 FR 45066, July 14, 2023]

§ 330.2 Pregnancy-nursing warning.

A pregnancy-nursing warning for OTC drugs is set forth under §201.63 of this chapter.

[47 FR 54758, Dec. 3, 1982]

§ 330.3 Imprinting of solid oral dosage form drug products.

A requirement to imprint an identification code on solid oral dosage form drug products is set forth under part 206 of this chapter.

[58 FR 47959, Sept. 13, 1993]

§ 330.5 Drug categories.

Monographs promulgated pursuant to the provisions of this part shall be established in this part 330 and following parts and shall cover the following designated categories:
(a) Antacids.
(b) Laxatives.

(c) Antidiarrheal products.
(d) Emetics.
(e) Antiemetics.
(f) Antiperspirants.
(g) Sunburn prevention and treatment products.
(h) Vitamin-mineral products.
(i) Antimicrobial products.
(j) Dandruff products.
(k) Oral hygiene aids.
(l) Hemorrhoidal products.
(m) Hematinics.
(n) Bronchodilator and antiasthmatic products.
(o) Analgesics.
(p) Sedatives and sleep aids.
(q) Stimulants.
(r) Antitussives.
(s) Allergy treatment products.
(t) Cold remedies.
(u) Antirheumatic products.
(v) Ophthalmic products.
(w) Contraceptive products.
(x) Miscellaneous dermatologic products.
(y) Dentifrices and dental products such as analgesics, antiseptics, etc.
(z) Miscellaneous (all other OTC drugs not falling within one of the above therapeutic categories).

Subpart B—Administrative Procedures

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

For purposes of classifying over-the-counter (OTC) drugs as drugs generally recognized among qualified experts as safe and effective for use and as not misbranded drugs, the following regulations shall apply:

(a) *Procedure for establishing OTC drug monographs*—(1) *Advisory review panels.* The Commissioner shall appoint advisory review panels of qualified experts to evaluate the safety and effectiveness of OTC drugs, to review OTC drug labeling, and to advise him on the promulgation of monographs establishing conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. A single advisory review panel shall be established for each designated category of OTC drugs and every OTC drug category will be considered by a panel. The members of a panel shall be qualified experts (appointed by the Commissioner) and may include persons from lists submitted by organizations representing professional, consumer, and industry interests. The Commissioner shall designate the chairman of each panel. Summary minutes of all meetings shall be made.

(2) *Request for data and views.* The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of OTC drugs. Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed monograph and the full report(s) of the panel or until the Commissioner places the panel's recommendations on public display at the office of the Dockets Management Staff. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the office of the Dockets Management Staff of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes. To be considered, eight copies of the data and/or views on any marketed drug within the class must be submitted, preferably bound, indexed, and on standard sized paper (approximately 8½ × 11 inches). When requested, abbreviated submissions should be sent. All submissions must be in the following format:

OTC DRUG REVIEW INFORMATION

I. Label(s) and all labeling (preferably mounted and filed with the other data—facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

IV. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports. Identify expected or frequently reported side effects.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports. Identify expected or frequently reported side effects.

4. Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports. Identify expected or frequently reported side effects.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished drug product.

5. Pertinent medical and scientific literature.

V. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports. Identify expected or frequently reported side effects.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports. Identify expected or frequently reported side effects.

4. Pertinent marketing experiences that may influence a determination on the efficacy of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports. Identify expected or frequently reported side effects.

4. Pertinent marketing experiences that may influence a determination on the efficacy of the finished drug product.

5. Pertinent medical and scientific literature.

VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

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.

(3) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner with respect to the safety and effectiveness of the drugs in a designated category of OTC drugs. A panel may consult any individual or group. Any interested person may request an opportunity to present oral views to the panel; such request may be granted or denied by the panel. Such requests for oral presentations should be in written form including a summarization of the data to be presented to the panel. Any interested person may present written data and

views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in paragraph (a)(2) of this section and within the time period established for the drug category in the notice for review by a panel.

(4) *Standards for safety, effectiveness, and labeling.* The advisory review panel, in reviewing the data submitted to it and preparing its conclusions and recommendations, and the Commissioner, in reviewing the conclusions and recommendations of the panel and the published proposed, tentative, and the final monographs, shall apply the following standards to determine general recognition that a category of OTC drugs is safe and effective and not misbranded:

(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(ii) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.126(b) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(iii) The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

(iv) An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

(v) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

(vi) A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs.

(5) *Advisory review panel report to the Commissioner.* An advisory review panel may submit to the Commissioner a report containing its conclusions and recommendations with respect to the conditions under which OTC drugs falling within the category covered by the panel are generally recognized as safe and effective and not misbranded. Included within this report shall be:

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

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

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

(6) *Proposed monograph.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing:

(i) A monograph or monographs 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 (Category I).

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

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

(iv) The full report(s) of the panel to the Commissioner. The proposed order shall specify a reasonable period of time within which conditions falling within paragraph (a)(6)(iii) of this section may be continued in marketed products while the data necessary to support them are being obtained for evaluation by the Food and Drug Administration. The summary minutes of the panel meetings shall be made available to interested persons upon request. Any interested person may, within 90 days after publication of the proposed order in the FEDERAL REGISTER, file with the Dockets Management Staff of the Food and Drug Administration written comments in triplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Dockets Management Staff between the hours of 9 a.m. and 4 p.m., Monday through Friday. Within 30 days after the final day for submission of comments, reply comments may be filed with the Dockets Management Staff; these comments shall be utilized to reply to comments made by other interested persons and not to reiterate a position. The Commissioner may satisfy this requirement by publishing in the FEDERAL REGISTER a proposed order summarizing the full report of the advisory review panel, containing its conclusions and recommendations, to obtain full public comment before undertaking his own evaluation and decision on the matters involved.

(7) *Tentative final monograph.* (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 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 Staff, Food and Drug Administration, written comments or

written objections specifying with particularity the omissions or additions requested. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(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 Staff, Food and Drug Administration, written objections specifying with particularity the provision of the tentative order to which objection is made. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(iii) Within 12 months after publishing a tentative order pursuant to paragraph (a)(7)(i) of this section, any interested person may file with the Dockets Management Staff, Food and Drug Administration, new data and information to support a condition excluded from the monograph in the tentative order.

(iv) Within 60 days after the final day for submission of new data and information, comments on the new data and information may be filed with the Dockets Management Staff, Food and Drug Administration.

(v) New data and information submitted after the time specified in this paragraph but prior to the establishment of a final monograph will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final monograph has been published in the FEDERAL REGISTER unless the Commisisoner finds that good cause has been shown that warrants earlier consideration.

(8) *Oral hearing before the Commissioner.* After reviewing objections filed in response to the tentative final monograph, the Commissioner, if he finds reasonable grounds in support thereof, shall by notice in the FEDERAL REGISTER schedule an oral hearing. The notice scheduling an oral hearing shall specify the length of the hearing and how the time shall be divided among the parties requesting the hearing. The hearing shall be conducted by the Commissioner and may not be delegated.

(9) *Final monograph.* After reviewing the objections, the entire administrative record including all new data and information and comments, and considering the arguments made at any oral hearing, the Commissioner shall publish in the FEDERAL REGISTER a final 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. The monograph shall become effective as specified in the order.

(10) *Administrative record.* (i) All data and information to be considered in any proceeding pursuant to this section shall be submitted in response to the request for data and views pursuant to paragraph (a)(2) of this section, in response to any other notice published in the FEDERAL REGISTER, or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section or submitted to the Dockets Management Staff as part of the comments during the 90-day period and 30-day rebuttal comment period permitted pursuant to paragraph (a)(6) of this section or submitted to the Dockets Management Staff during the 12-month period or as part of the comments during the 60-day period permitted pursuant to paragraph (a)(7) of this section.

(ii) The Commissioner shall make all decisions and issue all orders pursuant to this section solely on the basis of the administrative record, and shall not consider data or information not

included as part of the administrative record.

(iii) The administrative record shall consist solely of the following material: All notices and orders published in the FEDERAL REGISTER, all data and views submitted in response to the request published pursuant to paragraph (a)(2) of this section, in response to any other notice published in the FEDERAL REGISTER, or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section, all minutes of panel meetings, the panel report(s), all comments and rebuttal comments submitted on the proposed monograph and all new data and information submitted pursuant to paragraph (a)(6) of this section, all objections submitted on the tentative final monograph and all new data and information and comments submitted pursuant to paragraph (a)(7) of this section, the complete record of any oral public hearing conducted pursuant to paragraph (a)(8) of this section, all other comments requested at any time by the Commissioner, all data and information for which the Commissioner has reopened the administrative record, and all other material that the Commissioner includes in the administrative record as part of the basis for the Commissioner's decision.

(11) *Court appeal.* The monograph contained in the final order constitutes final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner may, at his discretion, stay the effective date for part or all of the monograph pending appeal and final court adjudication.

(12) *Amendment of monographs.* (i) The Commissioner may propose on the Commissioner's own initiative to amend or repeal any monograph established pursuant to this section. Any interested person may petition the Commissioner for such proposal pursuant to §10.30 of this chapter. The Commissioner may deny the petition if the Commissioner finds a lack of safety or effectiveness employing the standards in paragraph (a)(4) of this section (in which case the appeal provisions of paragraph (a)(11) of this section shall apply), or the Commissioner may publish a proposed amendment or repeal in the FEDERAL REGISTER if the Commissioner finds general recognition of safety and effectiveness employing the standards in paragraph (a)(4) of this section. Any interested person may, within 90 days after publication of the proposed order in the FEDERAL REGISTER, file with the Dockets Management Staff, Food and Drug Administration, written comments in triplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed in the Dockets Management Staff between the hours of 9 a.m. and 4 p.m., Monday through Friday. After reviewing the comments, the Commissioner shall publish a final order amending the monograph established under the provisions of paragraph (a)(9) of this section or withdraw the proposal if comments opposing the amendment are persuasive. A new drug application may be submitted in lieu of, or in addition to, a petition under this paragraph.

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

(b) *Regulatory action.* Any product which fails to conform to an applicable monograph after its effective date is liable to regulatory action.

(c) Information and data submitted under this section shall include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was

conducted in compliance with the good laboratory practice regulations set forth in part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

(d) [Reserved]

(e) *Institutional review and informed consent.* Information and data submitted under this section after July 27, 1981, shall include statements regarding each clinical investigation involving human subjects, from which the information and data are derived, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter, or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in part 50 of this chapter.

(f) *Financial certification or disclosure statement.* Any clinical data submitted under this section must be accompanied by financial certifications or disclosure statements or both as required by part 54 of this chapter.

[39 FR 11741, Mar. 29, 1974, as amended at 39 FR 39556, Nov. 8, 1974; 42 FR 19141, Apr. 12, 1977; 42 FR 54800, Oct. 11, 1977; 46 FR 8460, 8955, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981; 46 FR 21360, Apr. 10, 1981; 46 FR 47738, Sept. 29, 1981; 50 FR 7516, Feb. 22, 1985; 55 FR 11581, Mar. 29, 1990; 63 FR 5253, Feb. 2, 1998; 67 FR 3073, Jan. 23, 2002; 88 FR 45066, July 14, 2023]

§ 330.11 NDA deviations from applicable monograph.

A new drug application requesting approval of an OTC drug deviating in any respect from a monograph that has become final shall be in the form required by § 314.50 of this chapter, but shall include a statement that the product meets all conditions of the applicable monograph except for the deviation for which approval is requested and may omit all information except that pertinent to the deviation.

[39 FR 11741, Mar. 29, 1974, as amended at 55 FR 11581, Mar. 29, 1990]

§ 330.12 Status of over-the-counter (OTC) drugs previously reviewed under the Drug Efficacy Study (DESI).

(a) There were 420 OTC drugs reviewed in the Drug Efficacy Study (a review of drugs introduced to the market through new drug procedures between 1938 and 1962). A careful review has been made of the reports on these drugs to determine those drugs for which implementation may be deferred without significant risk to the public health, pending review by appropriate OTC drug advisory review panels and promulgation of a monograph.

(b) On and after April 20, 1972, a number of notices were published in the FEDERAL REGISTER concerning previously unpublished OTC drugs reviewed by the National Academy of Sciences-National Research Council Drug Efficacy Study Group. Only the evaluations and comments of the panels were published, with no conclusions of the Commissioner of Food and Drugs. Those publications were for the purpose of giving interested persons the benefit of the Academy's opinions. For those products, and also for OTC drug products previously published with the Commissioner's conclusions (except for the products listed in paragraphs (b) (1) and (2) of this section, all requests for data, revised labeling, requests for new drug applications, abbreviated new drug applications, updating supplements, data to support less than effective claims, if any, etc., are deferred, and such OTC drug products are instead subject to the OTC drug review in their appropriate classes pursuant to the procedures established in this subpart.

(1) The requirements of the following DESI announcements are not deferred (the reference document may also pertain to prescription drugs):

(i) Certain Surgical Sutures (DESI 4725), published in the FEDERAL REGISTER of November 11, 1971 (36 FR 21612).

(ii) Absorbable Dusting Powder (DESI 6264), published in the FEDERAL REGISTER of May 25, 1971 (36 FR 9475).

(iii) Certain Insulin Preparations (DESI 4286), published in the FEDERAL REGISTER of April 9, 1971 (36 FR 6842).

(iv) Sulfo-Van Ointment (DESI 2230), published in the FEDERAL REGISTER of October 8, 1970 (35 FR 15860).

(v) Antiperspirants and Deodorants Containing Neomycin Sulfate (DESI 11048) for which an order revoking provisions for certification or release was published in the FEDERAL REGISTER of December 5, 1972 (37 FR 25820) and has been stayed by the filing of objections.

(vi) Thorexin Cough Medicine (DESI 11160) for which a notice of opportunity for hearing was published in the FEDERAL REGISTER of February 2, 1973 (38 FR 3210).

(vii) Antibiotic susceptibility discs (DESI 90235) for which an order providing for certain discs to be certified and removing provisions for certification of other discs was published in the FEDERAL REGISTER of September 30, 1972 (37 FR 20525) and has been stayed by the filing of objections notice of which was published in the FEDERAL REGISTER of March 15, 1973 (38 FR 7007).

(2) Deferral of requirements is not appropriate when an announcement has been published and has been followed by a final order classifying a drug either as lacking substantial evidence of effectiveness or as not shown to be safe. These products will be removed from the market, if they have not already been removed. Regulatory action will also be undertaken against identical, similar and related products (21 CFR 310.6). Deferral of requirements is not appropriate for the following (the referenced document may also pertain to prescription drugs):

(i) Certain Sulfonamide-Decongestant Nasal Preparation (DESI 4850), for which notice of withdrawal of approval of new drug applications was published in the FEDERAL REGISTER of October 24, 1970 (35 FR 16605, 16606).

(ii) Eskay's Theranates, containing strychnine, sodium, and calcium glycerophosphates, thiamine hydrochloride, alcohol, and phosphoric acid (DESI 2220), for which notice of withdrawal of approval of the new drug application was published in the FEDERAL REGISTER of February 18, 1971 (36 FR 3152).

(iii) The following topical drugs (DESI 1726), for which notice of withdrawal of new drug applications was published in the FEDERAL REGISTER of August 28, 1971 (36 FR 17368):

(*a*) Rhulitol Solution, containing tannic acid, chlorobutanol, phenol, camphor, alum, and isopropyl alcohol.

(*b*) Zirnox Topical Lotion, containing phenyitoloxamine citrate and zirconium oxide.

(iv) Menacyl Tablets, containing aspirin, menadione, and ascorbic acid (DESI 6363), for which notice of withdrawal of approval of the new drug application was published in the FEDERAL REGISTER of July 23, 1970 (35 FR 11827).

(v) Curad Medicated Adhesive Bandage containing sulfathiazole (DESI 4964), for which notice of withdrawal of approval of the new drug application was published in the FEDERAL REGISTER of December 31, 1969 (34 FR 20441).

(vi) Drugs Containing Rutin, Quercetin, Hesperidin, or any Bioflavonoids (DESI 5960), for which notice of withdrawal of approval of new drug applications was published in the FEDERAL REGISTER of July 3, 1970 (35 FR 10872, 10873) and October 17, 1970 (35 FR 16332). A further notice of opportunity for hearing with respect to the drugs covered by the October 17, 1970 FEDERAL REGISTER notice will be published at a later date.

(vii) Antibiotics in Combination with Other Drugs for Nasal Use (DESI 7561), for which an order revoking provision for certification was published in the FEDERAL REGISTER of August 6, 1971 (36 FR 14469) and confirmed in the FEDERAL REGISTER of October 28, 1971 (36 FR 20686).

(viii) Antibiotic Troches (DESI 8328), for which an order revoking provision for certification was published in the FEDERAL REGISTER of July 14, 1971 (36 FR 13089) and confirmed in the FEDERAL REGISTER of October 9, 1971 (36 FR 19695).

(ix) Certain Drugs Containing Oxyphenisatin or Oxyphenisatin Acetate (DESI 10732), for which notices of withdrawal of approval of new drug applications were published in the FEDERAL REGISTER of February 1, 1972 (37 FR 2460), and March 9, 1973 (38 FR 6419).

(x) Curad Medicated Adhesive Bandage containing tyrothricin-nitrofurazone (DESI 6898), for which an order revoking provision for certification was published March 14, 1972 (37 FR

5294), and confirmed in the FEDERAL REGISTER of July 6, 1972 (37 FR 13254).

(xi) Candette Cough Gel (DESI 11562), for which notice of withdrawal of approval of the new drug application was published in the FEDERAL REGISTER of November 19, 1972 (37 FR 25249).

(xii) Certain OTC Multiple-Vitamin Preparations for Oral Use containing excessive amounts of vitamin D and/or vitamin A (DESI 97), for which notice of withdrawal of approval of the new drug applications was published in the FEDERAL REGISTER of November 29, 1972 (37 FR 25249).

(xiii) Certain Sulfonamide-Containing Preparations for Topical Ophthalmic or Otic Use (DESI 368, for which a notice of withdrawal of approval was published in the FEDERAL REGISTER of February 2, 1973 (38 FR 3208).

(xiv) Those parts of the publication entitled ''Certain Mouthwash and Gargle Preparations'' (DESI 2855) pertaining to Tyrolaris Mouthwash, containing tyrothricin, panthenol, and alcohol, for which an order revoking provision for certification was published in the FEDERAL REGISTER of February 2, 1967 (32 FR 1172) prior to the drug efficacy study implementation.

(c) Manufacturers and distributors should take notice that the information on OTC drugs provided by the Drug Efficacy Study review is valuable information as to the deficiencies in the data available to support indications for use. They are encouraged to perform studies to obtain adequate evidence of effectiveness for the review of OTC drugs which is already in progress. In the interim it is in the public interest that manufacturers and distributors of all OTC drugs effect changes in their formulations and/or labeling to bring the products into conformity with current medical knowledge and experience.

(d) Manufacturers and distributors of OTC drugs may be reluctant to make appropriate formulation and/or labeling changes for fear of losing the protection of the so-called ''grandfather'' provisions of the 1938 Federal Food, Drug, and Cosmetic Act (sec. 201(p)(1)) and the 1962 amendments to the act (sec. 107(c) of those amendments). To encourage and facilitate prompt changes, the Food and Drug Administration will not take legal action against any OTC drug, other than those not deferred, based on a charge that the product is a new drug and not grandfathered under the act as a result of the changes if the changes in formulation and/or labeling are of the following kind:

(1) The addition to the labeling of warning, contraindications, side effects, and/or precaution information.

(2) The deletion from the labeling of false, misleading, or unsupported indications for use or claims of effectiveness.

(3) Changes in the components or composition of the drug that will give increased assurance that the drug will have its intended effect, yet not raise or contribute any added safety questions.

(4) Changes in the components or composition of the drug which may reasonably be concluded to improve the safety of the drug, without diminishing its effectiveness.

(e) The forbearance from legal action for lack of grandfather protection is an interim procedure designed to encourage appropriate change in formulation and/or labeling during the time period required to review the various classes of OTC drugs. At such time as an applicable OTC drug monograph becomes effective, the interim procedure will automatically be terminated and any appropriate regulatory action will be initiated.

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

(a) Before the publication in the FEDERAL REGISTER of an applicable proposed monograph, 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 an OTC drug product on December 4, 1975, shall be regarded as a new drug within

the meaning of section 201(p) of the act for which an approved new drug application is required.

(b)(1) An OTC drug product that contains: (i) 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

(ii) An active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by the panel in category I (conditions subject to §330.10(a)(6)(i)) shall be regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application is required if marketed for OTC use prior to the date of publication in the FEDERAL REGISTER of a proposed monograph.

(2) An OTC drug product covered by paragraph (b)(1) of this section which is marketed after the date of publication in the FEDERAL REGISTER of a proposed monograph but prior to the effective date of a final monograph shall be subject to the risk that the Commissioner may not accept the panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. The Commissioner may state such position at any time by notice in the FEDERAL REGISTER, either separately or as part of another document; appropriate regulatory action will commence immediately and will not await publication of a final monograph. Marketing of such a product with a formulation or labeling not in accord with a proposed monograph or tentative final monograph also may result in regulatory action against the product, the marketer, or both.

(c) 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 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 Dockets Management Staff 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 Dockets Management Staff.

(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 Staff.

(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 Dockets Management Staff 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 Dockets Management Staff. 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; 88 FR 45066, July 14, 2023]

§ 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:

(i) Include the condition in an appropriate OTC monograph(s), either by amending an existing monograph(s) or establishing a new monograph(s), if necessary; or

(ii) Include the condition in § 310.502 of this chapter.

(5) Within 912 days of the closing of the docket of the proposed rulemaking under paragraph (c)(4) of this section, FDA will issue a final rule.

[81 FR 84477, Nov. 23, 2016]

PART 331—ANTACID PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Testing Procedures

Subpart D—Labeling

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

SOURCE: 39 FR 19874, June 4, 1974, unless otherwise noted.

Subpart A—General Provisions

§ 331.1 Scope.

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