Guidance for Industry
Time and Extent Applications

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)

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This draft guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

A. What does this guidance cover?

This guidance is intended to explain how and what information an applicant would submit to FDA for a drug product to be considered for review in the over-the-counter (OTC) drug monograph system. FDA regulations (21 CFR 330.14) set forth additional criteria and procedures by which OTC drugs (i.e., those drugs initially marketed in the United States after the OTC drug review began in 1972 and those drugs without any U.S. marketing experience) can be considered in the OTC drug monograph system. Under the regulations (21 CFR 330.14(c)), certain information must be submitted in a time and extent application (TEA) to show that a drug product has been marketed OTC *to a material extent* and *for a material time*. This document describes the information and format of a TEA that is used to determine if such drug products have been marketed OTC *to a material extent* and *for a material time*. Drug products covered by this guidance are those OTC drug products that (1) were initially marketed in the United States after the OTC drug review began in 1972, or (2) are without any U.S. marketing experience.

B. What OTC *conditions* are covered by this guidance?

Under the regulation (21 CFR 330.14(a)), a *condition* refers to an active ingredient or botanical drug substance (or combination of both), dosage form, dosage strength, or route of administration marketed for a particular OTC use. This list includes conditions regulated as cosmetic products or dietary supplements in a foreign country that would be regulated as OTC products in the United States. Conditions subject to this guidance are those that are ***not*** covered by existing OTC drug monographs (i.e., those conditions marketed in the United States after the beginning of the OTC drug review in 1972 or those without any U.S. marketing experience).

[1] This guidance has been prepared by the Division of Over-the-Counter Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

C. Is a TEA the only information I would submit to have my *condition* included in a monograph?

Submission of TEA information is the first step in a two-step process. FDA uses the TEA to determine if a condition is eligible to be considered for inclusion in the OTC drug monograph system. Under 21 CFR 330.14(e), if a condition is found to be eligible, a notice of eligibility is published in the *Federal Register*, and the Agency would send the notice to the applicant. Under 21 CFR 330.14(f), the notice would request interested persons to submit data demonstrating the safety and efficacy of the condition for its intended OTC use, and the TEA would be placed on public display. The submission of any such data is the second step in this process. The Agency would then review the data received and determine whether the condition would be added to an existing or newly created OTC drug monograph.

II. BACKGROUND

A. Where can I find the regulations concerning OTC drug monographs and TEAs?

Part 330 (21 CFR part 330) describes the monograph criteria and procedures for classifying OTC drug products as *generally recognized as safe and effective and not misbranded*. The ***additional*** criteria and procedures (i.e., for the TEA) described in this guidance were published as an amendment to part 330 in the *Federal Register* of January 23, 2002 (67 FR 3060), with an effective date of February 22, 2002. TEA requirements are contained in § 330.14. A copy of the final rule can be found on the Internet at http://www.fda.gov/OHRMS/DOCKETS/98fr/012302a.pdf.

B. How were *conditions* previously added to an OTC drug monograph?

Previously, if an OTC drug condition had been marketed solely in a foreign country, a firm was required to submit a new drug application (NDA) before the condition could be marketed in the United States. Companies also were required to submit an NDA if their OTC drug products were initially marketed in the United States after the beginning of the OTC drug review in 1972. Conditions covered by existing proposed or final OTC drug monographs were (and are still) handled through the submission of a citizen petition as described in § 10.30 (21 CFR 10.30).

C. Who can submit a TEA?

Any interested party can submit a TEA.

III. WOULD I SUBMIT AN NDA, CITIZEN PETITION, OR TEA?

A. NDA

An applicant can submit an NDA for a new OTC drug condition (see 21 CFR part 314). An applicant can also submit an NDA to request approval of an OTC drug product that deviates in any respect from a monograph that has become final (see 21 CFR 330.11). An NDA seeks approval of a ***specific product*** that is formulated and labeled as it is to be marketed. Benefits of this approach include (1) confidentiality during the approval process; (2) a period of marketing exclusivity upon approval if certain conditions are met; and (3) historically, less time for review of the application from submission to a final decision, compared to other routes of approval (i.e., citizen petitions and TEAs). However, as described in part 314, an NDA (1) generally requires a monetary fee, (2) is approved only for a specific product (including formulation and labeling), (3) has reporting requirements subsequent to approval, and (4) requires prior approval for most subsequent labeling and formulation changes to the product.

B. Citizen Petition

A citizen petition is the appropriate process to request amendment or repeal of conditions covered by proposed or final OTC drug monographs (see 21 CFR 10.30 and 330.10(a)(12)). However, this process cannot be used to request that conditions be considered for inclusion in the OTC drug monograph system. For FDA to approve the petition request, accompanying data must demonstrate general recognition of safety and effectiveness in accordance with § 330.10. If FDA believes the request should be granted, the Agency could issue a notice of proposed rulemaking (proposed rule) that states the proposed action and explains the reason for the action. FDA would then receive comments to the proposed rule, review these comments, and publish a final rule that would amend the monograph or withdraw the proposed rule. All steps in the petition process are open to the public, and petitions do not require payment of a monetary fee to FDA. Although response letters are generally sent to the sponsor of a petition within 180 days, the public rulemaking process to amend the monograph for an OTC drug product historically has taken more time than a final decision on an NDA. After a condition has been incorporated into the final monograph for an OTC drug product (or in a notice of enforcement policy under 21 CFR 330.14(h)), if a finalization of the monograph is not imminent), it can be marketed by any interested party without prior approval by FDA.

C. TEA

The purpose of a TEA is to request that conditions be considered for inclusion in the OTC drug monograph system. A TEA would only be submitted for conditions that the applicant believes have been marketed OTC *to a material extent* and *for a material time* as follows:

- conditions initially marketed (under an NDA) in the United States after the OTC drug review began in 1972

- conditions marketed only outside the United States (and that would be regulated as OTC drugs in the United States)

- conditions not generally recognized as safe and effective (i.e., *nonmonograph*) in the original OTC drug review but conditions for which additional data and information are being presented

Under § 330.14(b), the conditions must be marketed for OTC purchase by consumers and for at least 5 continuous years in the same country in sufficient quantity (although more than one country may be appropriate depending on the extent of marketing). The TEA is only the first step in a two-step process. If a condition is determined to be eligible for inclusion in the monograph system, the TEA would be placed on public display and a notice of eligibility would be published in the *Federal Register*. This notice would request data that demonstrate general recognition of safety and efficacy for the condition. The submission of any data is the second step in the process.

After reviewing the data, if appropriate, FDA would publish a proposed rule and then a final rule incorporating the new condition. Similar to a petition, FDA would typically respond to a TEA within 180 days, and a monetary fee would not be required. After a condition has been incorporated into a final monograph (or in a notice of enforcement policy under 21 CFR 330.14(h), if a finalization of the monograph is not imminent), the condition could be marketed by any interested party without prior approval by FDA. For marketing to occur, § 330.14(i) requires that the active ingredient or botanical drug substance be recognized in the U.S. Pharmacopeia-National Formulary (USP-NF).

IV. WHAT DO I NEED TO KNOW ABOUT THE CONTENT OF THE TEA?

A. What information must be included about the condition?

Under § 330.14(c)(1), all TEAs must include the following information:

- description of the active ingredients or botanical drug substances
- pharmacological classes
- intended OTC uses
- OTC strengths
- dosage forms
- routes of administration
- directions for use
- applicable OTC drug monograph or rationale for a new monograph

Reference to the current edition of the USP-NF or foreign compendia may help satisfy the requirements of this section of the regulation.

B. Do I need to list every country in which the condition is marketed and include the marketing information listed in § 330.14(c)(2) for each country?

Under § 330.14(c)(2), the applicant must provide a list of ***all*** countries in which the condition has been marketed. If the condition is marketed OTC in four or fewer countries, the applicant must include the following information required under § 330.14(c)(2) for each country:

- how the condition has been marketed
- the cumulative total number of dosage units sold for each dosage form of the condition
- a description of the population demographics and the source or sources from which this information has been compiled
- any use pattern differences between countries
- a description of each country's system for identifying adverse drug experiences

Under § 330.14(c)(4), if the condition is marketed in five or more countries (with a minimum of 5 continuous years of marketing in at least one country), then the applicant may select at least five of these countries from which to submit the required information, under § 330.14(c)(2). Under § 330.14(c)(4), the 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. The Agency recommends that the number of countries for which all § 330.14(c)(2) information is submitted be based on those countries that are most likely to support eligibility. Additionally, under § 330.14(c)(4), applicants should explain in the TEA the basis for the countries selected.

Under §§ 330.14(c)(5) and (c)(6), the information on certain categories (e.g., prescription-only sales and marketing withdrawals or denials) must be reported for all countries in which the condition has been marketed, even if the information required under § 330.14(c)(2) is only given for five countries.

C. If a condition is marketed in a country as a nonprescription pharmacy-only product, can this information be used to support marketing of the condition *for OTC purchase by consumers*?

Under § 330.14(b)(1), if the product is sold only in a pharmacy, with or without involvement of a pharmacist, the applicant must establish that this marketing restriction does not indicate safety concerns about (1) its toxicity or other potentially harmful effects, (2) the method of its use, or (3) the collateral measures necessary to its use.

D. Do I need to submit information about the number of dosage units sold and copies of retail labeling even if I am not the manufacturer or supplier of a finished dosage form?

Under §§ 330.14(c)(2)(ii) and (c)(3), respectively, TEA applicants must submit the number of dosage units and copies of retail labeling, even if they are not the manufacturer or supplier of a finished dosage form. However, the manufacturers and suppliers of bulk OTC active ingredients may submit information on dosage unit as the total weight of active ingredient sold and submit information on potential consumer exposure in accordance with the calculations provided in § 330.14(c)(2)(ii). Manufacturers or suppliers of bulk OTC active ingredients must also submit a copy of current finished product labeling and provide the information about labeling as listed in § 330.14(c)(3). Applicants need not submit a copy of every label used in a country and related to the condition if the labeling information for that country (i.e., active ingredients and corresponding dosage strengths, indications, warnings, and directions for use) is essentially the same.

E. What is *use pattern* information and when would I include it in the TEA?

Use pattern refers to how often a drug product can be used (according to the label) and for how long. Under § 330.14(c)(2)(iv), if the use pattern varies between countries or changes have occurred over time in one or more countries, then the applicant must describe the use pattern for each country and provide information on why there are differences or changes.

F. Would I submit reports from countries regarding adverse drug experience?

Reports on adverse drug experience do not need to be submitted with the TEA. However, the Agency encourages the applicant to describe the country's system for identifying adverse drug experiences, especially those found in OTC marketing experience. We recommend that the applicant include in this description how the information is collected, if applicable. The applicant can submit information on adverse drug experiences in response to the request for data upon publication of a notice of eligibility (i.e., if the condition is determined to be eligible for inclusion in the OTC drug monograph system).

G. What product labeling information would I include in the TEA?

According to § 330.14(c)(3), the applicant must include an English version of the current product labeling from each country in which the condition has been marketed. For each example of product labeling, the regulation requires that the applicant include a statement of (1) how long the condition has been marketed; (2) how long the current labeling has been in use; and (3) whether the current labeling has or has not been authorized, accepted, or approved by a regulatory body in each country where marketed. Applicants need not submit a copy of every label used in a country and related to the condition if the labeling information for that country is essentially the same.

H. Am I required to include only OTC marketing information for currently marketed drug products?

The applicant must include other marketing information, when appropriate. Sections 330.14(c)(5) and (c)(6) require the listing of specific information (1) when the condition is marketed only as a prescription drug in a country and (2) when the condition has been withdrawn from marketing or an application for OTC marketing has been denied.

I. What information is not required if the TEA is for an OTC drug product that has been marketed for more than 5 years in the United States?

If the TEA is for an OTC drug product that has been marketed in the United States for more than 5 years, it does not require the following:

- information on how the condition has been marketed
- the population demographics
- a description of the reporting system for adverse drug experience
- the product labeling information
- a list of all countries where the condition is marketed only as a prescription drug

All other information required under § 330.14(c) must be included in the TEA.

J. How can I obtain the appropriate information on population demographics for each country?

The following Web sites are two examples of sources that provide population demographics information: http://www.cia.gov/cia/publications/factbook/index.html and http://www.state.gov/www/background/index.html. The national statistical office for a particular country may also provide relevant information.

V. WHAT FORMAT WOULD I USE IN THE TEA?

A. Information describing the condition

The basic information and a detailed description of the ingredient or ingredients required by § 330.14(c)(1) can be presented in any format. It would be appropriate to include this information at the beginning of the TEA to clearly identify the purpose of the application before providing particular marketing information. Although not required, FDA recommends that the applicant present this information in a table format with any attachments following the table (for an example, see Table 1).

Table 1. Basic Information Describing New Condition

Active ingredient or botanical drug substance	
Pharmacological class	
Intended OTC use	
Strength	
Dosage form	
Route of administration	
Directions for use	
Current OTC drug monograph under which the condition would be marketed or request and rationale for creation of a new OTC drug monograph	
Active Ingredient Description	
Chemical and physical characteristic	
Method of synthesis or isolation	
Method of purification	
Additional specifications or analytical methods	
References to USP-NF or foreign compendia	
Botanical Drug Substance	
Identification of plant, plant part, alga, or fungus	
Grower and/or supplier identification	
Growth conditions	
Harvest location and harvest time	
Drug substance name	
Drug substance appearance	
Chemical and physical properties	
Chemical constituents	
Biological activity	
Active constituents (or chemical markers) - qualitative and quantitative descriptions	
Type of manufacturing process	
Any further processing information	
References to USP-NF or foreign compendia	

B. Information listed by country (including the United States)

Certain information requested for each country must be submitted in a table format (see § 330.14(c)(7)). However, FDA recommends that the applicant include as much of the TEA information as possible in a table with other information (e.g., labeling) as attachments. Table 2 is an example of a table that could be included for *each* country.

Table 2. Information Describing Marketing Experience by Country

Country	
Marketing status (If limited to pharmacy sale, list reason why and collateral measures.)[1,2]	
Length of current marketing status[1,2]	
Population demographics[1,2]	
Cumulative total number of dosage units sold for each dosage form[2]	
Labeled use pattern, as applicable[2]	
Label approval[2]	
System for identifying adverse drug experiences (ADRs)[1]	

[1]Not necessary for U.S. marketing experience.
[2]Section 330.14(c)(7) states that this information must be included in a table.

C. Summary of marketing experience

In addition to the required information specific to each country, FDA recommends that the applicant also submit this information as a comparison of marketing experience between countries. Some of this comparison information would be more appropriate for a paragraph format. However, some of the information can be summarized for each country in table format to ease comparisons between countries. An example of the information that may be appropriate for a summary table is shown in Table 3.

Table 3. Summary of Marketing Experience

	Country 1	Country 2	Country 3	Country 4	Country 5
Marketing status					
Years of marketing status					
Cumulative number of dosage units					
Labeled use pattern, if applicable					

VI. WHAT ELSE DO I NEED TO KNOW ABOUT A TEA?

A. Where would I submit the TEA and how many copies?

The applicant would mail three copies of the TEA to the Central Document Room, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Clearly identify the submission as a Confidential Time and Extent Application (TEA). FDA recommends that the applicant call the Division of Over-the-Counter Drug Products 2 weeks after submitting the TEA to ensure that the Agency has received the TEA. The phone number for the Division of Over-the-Counter Drug Products can be found at http://www.fda.gov/cder/otc/default.htm.

B. Is confidentiality protected?

If the TEA contains confidential information, the applicant must clearly identify any information that is considered confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)) (see § 330.14(d)). All applications would be handled as confidential upon receipt. If the condition were found to be eligible for inclusion in the OTC drug monograph system, any information deemed confidential by the Agency would be removed from the TEA, and the remainder of the application would be placed on public display. If the condition is not found to be eligible, the TEA would not be placed on public display, but a letter from FDA to the applicant stating why the condition was not found to be acceptable would be placed on public display in the Division of Dockets Management.