Guidance for Industry

Time and Extent Applications for Nonprescription Drug Products

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

September 2011
OTC

Guidance for Industry

Time and Extent Applications for Nonprescription Drug Products

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

September 2011
OTC

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1] Time and Extent Applications for Nonprescription Drug Products

This 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. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to explain what information an applicant should submit to the Food and Drug Administration (FDA) to request that a drug product be included in the over-the-counter (OTC) drug monograph system and to describe the process for submitting that information. FDA regulations set forth criteria and procedures by which OTC drugs that initially were 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 for inclusion in the OTC drug monograph system (21 CFR 330.14). The regulations establish a two-part process. First, to determine whether a drug product is eligible to be considered for inclusion in the OTC drug monograph system, certain information must be submitted in a time and extent application (TEA) to show that a drug product can meet the statutory standard of marketing *to a material extent* and *for a material time*.[2] Second, if the drug product is found eligible to be considered for inclusion in the OTC drug monograph system, we will publish a notice of eligibility in the *Federal Register* that requests that interested persons submit data to demonstrate the safety and effectiveness of the drug product for its OTC use(s) (21 CFR 330.14(e) and (f)).

This guidance describes the format and content of a TEA that is used to determine if a drug has been marketed OTC *to a material extent* and *for a material time*, and what happens after a TEA

[1] This guidance has been prepared by the Division of Nonprescription Regulation Development in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For a drug to not be a "new drug" under section 201(p)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the drug must have been marketed "to a material extent" and "for a material time" under its conditions for use. FDA regulations at 21 CFR 330.14 explain what applicants must submit to establish that an OTC drug has been marketed to a material extent and for a material time, thereby qualifying it to be eligible to be considered for inclusion in the OTC drug monograph system. See 21 CFR 330.14(b) and (c) and the final rule "Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded" (67 FR 3060, January 23, 2002).

is submitted. 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 on May 11, 1972; or (2) are without any U.S. marketing experience.

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.

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 (GRASE) and not misbranded*. The *additional* criteria and procedures, for OTC drug products initially marketed in the United States after the OTC drug review began in 1972 or without any U.S. marketing experience, which are described in this guidance, can be found at 21 CFR 330.14. These regulations were established in an amendment to part 330 in the *Federal Register* in 2002 (67 FR 3060). You can find a copy of the final rule on the Internet at http://www.fda.gov/OHRMS/DOCKETS/98fr/012302a.pdf.

B. What is an OTC condition?

The TEA regulations state that, for the purposes of 21 CFR 330.14, a *condition* means 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. Under this definition, conditions include products regulated as cosmetic products or dietary supplements in a foreign country that would be regulated as OTC drug products in the United States.

C. What OTC conditions are covered by this guidance?

Conditions subject to this guidance are 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 (21 CFR 330.14(a)). These conditions have not been previously evaluated for eligibility for inclusion in the OTC drug monograph system or general recognition of safety and effectiveness, and are not addressed in 21 CFR 310.545, current tentative final monographs, or current final monographs (21 CFR parts 331-358).

D. How were conditions added to an OTC drug monograph before 21 CFR 330.14 was established?

Before 21 CFR 330.14 was published in 2002, many conditions covered by this guidance could not be added to an OTC drug monograph and instead could be marketed only under an approved

application pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). If an OTC drug condition had been marketed solely in a foreign country, a company was required to obtain premarket approval under section 505 of the FD&C Act before the condition could be marketed in the United States. Companies also were required to obtain premarket approval under section 505 of the FD&C Act if their OTC drug products were initially marketed in the United States after the beginning of the OTC drug review in 1972.

E. Who can submit a TEA?

Any interested party can submit a TEA.

F. Is a TEA the only information I should submit to have my condition included in a monograph?

No, submission of the TEA is the first step in a two-step process to include a new condition in a monograph:

1. Time and Extent Application: As explained in more detail in section III.C. of this guidance, a TEA should provide the information needed to determine if a condition is ***eligible*** to be considered for inclusion in the OTC drug monograph system (21 CFR 330.14(c)).

2. Safety and Effectiveness Data Submission: If we review a TEA and determine that a condition is eligible for inclusion in the OTC drug monograph system, we will publish a notice of eligibility that requests the submission of data to demonstrate general recognition of the safety and effectiveness of the condition, and place the TEA on public display (21 CFR 330.14(e) and (f)). We then evaluate the safety and effectiveness data submitted using the standards in 21 CFR 330.10(a)(4) (21 CFR 330.14(g)).

G. Why can't I submit safety and effectiveness data with my TEA?

We believe that a two-step process, as described in section II.F., is the most efficient and appropriate method for us to determine whether a condition is acceptable for inclusion in the OTC drug monograph system. This two-step process has the following advantages:

- It prevents applicants from incurring unnecessary costs for developing safety and effectiveness data for a condition that may not meet basic eligibility requirements

- It avoids expending FDA resources evaluating safety and effectiveness data for a condition that does not meet the basic eligibility criteria

- It provides all interested parties (not just the applicant) an opportunity to submit safety and effectiveness data and information

III. SHOULD I SUBMIT AN APPLICATION UNDER SECTION 505 OF THE FD&C ACT, CITIZEN PETITION, OR TEA?

A. Application under section 505 of the FD&C Act

An applicant can submit an application under section 505 of the FD&C Act for a new OTC drug condition.[3] An applicant can also submit an application under section 505 to request approval of an OTC drug product that deviates in any respect from a monograph that has become final (21 CFR 330.11). An application under section 505 of the FD&C Act seeks approval of a *specific product* that is formulated and labeled as it is to be marketed (21 CFR 314.50). Benefits of this approach may include the following:

- Confidentiality during the approval process (21 CFR 314.430)
- A period of marketing exclusivity, for certain applications, upon approval if certain conditions are met (21 CFR 314.108)
- Historically, less time for review of the application from submission to a final decision, compared to other routes to market drugs (i.e., citizen petitions and TEAs)[4]

However, an application under section 505 of the FD&C Act generally includes the following:

- Approval only for a specific drug product (including formulation and labeling) (21 CFR 314.50 and 314.94)
- Reporting requirements subsequent to approval, in addition to adverse event reporting (21 CFR 314.80, 314.81, and 314.98)[5]
- Prior approval requirements for certain subsequent labeling and formulation changes to the drug product (21 CFR 314.70 and 314.97)

Certain applications are also subject to required fees (sections 735 and 736 of the FD&C Act).

[3] See section 505 of the FD&C Act and 21 CFR part 314.

[4] See 21 CFR 314.100 for a description of the time frames for review of applications.

[5] We note that there are some reporting requirements for OTC drugs marketed under a monograph. Under section 760 of the FD&C Act, manufacturers, packers, and distributers of OTC drugs marketed under a monograph are required to report certain kinds of information about serious adverse events associated with their drugs. See the guidance for industry *Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

B. Citizen petition

A citizen petition may be used to request the amendment or repeal of conditions covered by proposed or final OTC drug monographs (21 CFR 10.30 and 21 CFR 330.10(a)(12)). The citizen petition process should not be used to make an initial request to include in the OTC drug monograph system conditions marketed in the United States after the beginning of the OTC drug review in 1972 or those without any U.S. marketing experience; these must first be determined to be eligible for potential inclusion through submission of a TEA in accordance with 21 CFR 330.14.[6]

FDA regulations (21 CFR 330.10(a)(12)) explain the process by which we may amend or repeal an existing monograph in response to a citizen petition. We may grant a petitioner's request to amend or repeal a condition covered by an existing monograph if the petitioner's request is supported by adequate accompanying data (21 CFR 330.10(a)(12)). For example, if a petitioner requests that a condition be amended, we may grant the request if the petition is accompanied by data that demonstrate general recognition of safety and effectiveness of the amended condition in accordance with 21 CFR 330.10. If we believe a request should be granted, we will issue a notice of proposed rulemaking (proposed rule) that states the proposed action and explains the reason for the action. Any interested person would then have the opportunity to comment on the proposed rule, we would review these comments, and then publish a final rule that amends the monograph or withdraws the proposed rule (21 CFR 330.10(a)(12)(i)).

This citizen petition process is open to the public and does not require payment of a fee to the FDA. However, the process of filing a citizen petition that leads to a public rulemaking process to amend the monograph for an OTC drug product historically has taken more time than a final decision on a new drug application (NDA).

C. TEA

The purpose of a TEA is to request that we determine whether a condition is eligible for inclusion in the OTC drug monograph system. A TEA should be submitted only for conditions that the applicant believes have been marketed OTC *to a material extent* and *for a material time* (67 FR 3060). Under 21 CFR 330.14, a TEA may be submitted for:

- Conditions initially marketed (under an approved application under section 505 of the FD&C Act) in the United States after the OTC drug review began in 1972[7]

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

[6] If a condition is found eligible for potential inclusion in a monograph based on the submission of a TEA, it is not necessary to submit a citizen petition to request that the condition be considered for inclusion in a monograph (see section VII). However, after the safety and effectiveness data for such a condition has been submitted and the FDA has made a determination regarding the condition's safety and effectiveness and either included it in a monograph or in 21 CFR 310.502, a citizen petition may then be used to request additional changes to the monograph.

[7] See also 67 FR 3060.

To be eligible for inclusion in the OTC drug monograph system, a condition must be marketed for OTC purchase by consumers (21 CFR 330.14(b)). In addition, the condition must have been marketed OTC for at least 5 continuous years in the same country in sufficient quantity (although marketing in more than one country may be necessary depending on the extent of marketing) (21 CFR 330.14(b)).

As explained in section II.F., 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 will be placed on public display and a notice of eligibility will be published in the *Federal Register* (21 CFR 330.14(e)). This notice will request data that demonstrate general recognition of safety and effectiveness for the condition (21 CFR 330.14(f)). The safety and effectiveness data submission and evaluation is the second step in the process (21 CFR 330.14(f)). After reviewing the safety and effectiveness data, if we initially determine that the condition is GRASE for OTC use in the United States, we will publish a proposed rule to incorporate the new condition into an existing monograph, or create a new monograph if necessary (21 CFR 330.14(g)(3)). After considering comments and other information submitted regarding the proposed rule, we will publish a final rule, or reproposal if necessary, in the *Federal Register* (21 CFR 330.14(g)(5)).

We typically make an eligibility determination within 1 year of receiving a TEA, and a fee is not required. After a condition has been incorporated into a final monograph (or, if a finalization of the monograph is not imminent, has been subject to a notice of enforcement policy in accordance with 21 CFR 330.14(h)), the condition may be marketed in accordance with the applicable monographs by any interested party without prior approval by us (21 CFR 330.14(h)). For inclusion in a final monograph or in a notice of enforcement policy, 21 CFR 330.14(i) requires that the active ingredient or botanical drug substance be recognized in an official U.S. Pharmacopeia-National Formulary (USP-NF) drug monograph that sets forth its standards for identity, strength, quality, and purity.

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

A. What information must be included about the condition?

All TEAs must include the basic information required under 21 CFR 330.14(c)(1), including:

- A description of the active ingredients or botanical drug substances
- Pharmacologic classes
- Intended OTC uses
- OTC strengths
- OTC dosage forms
- Routes of administration

- Directions for use

- Applicable OTC drug monograph or request and rationale for creation of a new monograph

Reference to the USP-NF or a foreign compendium may satisfy, or help to satisfy, the requirements in 21 CFR 330.14(c)(1)(i) and (ii) for a detailed description of an active ingredient or botanical substance (21 CFR 330.14(c)(1)(iii)). If reference to the USP-NF or a foreign compendium is sufficient to satisfy these requirements, we expect that the method of synthesis and other confidential information would not ordinarily need to be included in the TEA.

B. Do I need to list every country in which the condition is marketed?

Under 21 CFR 330.14(c)(2), the applicant is required to provide a list of *all* countries in which the condition has been marketed.

C. What information is not required if the TEA is for an OTC drug product that has been marketed under an FDA-approved application for more than 5 years in the United States?

Under 21 CFR 330.14(c)(8), if the TEA is for an OTC drug product that has been marketed under an FDA-approved application in the United States for more than 5 years, it is not required to include the following information for any country:

- Information on how the condition has been marketed required under 21 CFR 330.14(c)(2)(i)

- A description of the population demographics required under 21 CFR 330.14(c)(2)(iii)

- A description of the reporting system for adverse drug experiences required under 21 CFR 330.14(c)(2)(v)

- Product labeling information required under 21 CFR 330.14(c)(3)

- 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, as required under 21 CFR 330.14(c)(5)

All other information required under 21 CFR 330.14(c) must be included in the TEA.

D. Do I need to include the marketing information listed in 21 CFR 330.14(c)(2) for each country in which the condition is marketed?

The number of countries in which the condition is marketed, and whether the drug product has been marketed OTC under an FDA-approved application for more than 5 years in the United

States (see section IV.C.), determines whether marketing information listed in 21 CFR 330.14(c)(2) must be submitted for each country. If the condition is marketed OTC in four or fewer countries (and has not been marketed OTC under an FDA-approved application for more than 5 years in the United States), the applicant must include the following general types of information required under 21 CFR 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, and, if there are use pattern differences, an explanation of why those differences exist
- A description of each country's system for identifying adverse drug experiences

Under 21 CFR 330.14(c)(2), there is more detail about what specific information should be provided in each of the above listed areas.

Under 21 CFR 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 five (or more) countries from which to submit the information required under 21 CFR 330.14(c)(2). Under 21 CFR 330.14(c)(4), the selected countries must include a 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. In addition, if the condition meets these criteria in any countries listed in section 802(b)(1)(A) of the FD&C Act, some of those countries should be included among the five selected (21 CFR 330.14(c)(4)). We recommend that the countries for which all 21 CFR 330.14(c)(2) information is submitted include those countries that have the most marketing experience because they are most likely to support eligibility. Additionally, under 21 CFR 330.14(c)(4), applicants should explain in the TEA the basis for the countries selected.

Under 21 CFR 330.14(c)(3) and (c)(5), information in certain categories (e.g., copies of labeling, and prescription-only sales) must be reported for all countries in which the condition has been marketed, even if the information required under 21 CFR 330.14(c)(2) is only given for five countries, unless the condition has been marketed OTC under an FDA-approved application for more than 5 years in the United States. The information required under 21 CFR 330.14(c)(6) must be for all countries in which the condition has been marketed, even if the information required under 21 CFR 330.14(c)(2) is only given for five countries or the condition has been marketed OTC under an FDA-approved application for more than 5 years in the United States.

E. Is a condition that is marketed in a country as a nonprescription pharmacy-only drug product eligible to be considered for inclusion in the OTC monograph system?

Such a condition may be eligible to be considered for inclusion in the OTC drug monograph system. Under 21 CFR 330.14(b)(1), if the drug product is sold only in a pharmacy, with or without involvement of a pharmacist, in addition to demonstrating that the drug product meets the other applicable criteria, 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.

F. 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 21 CFR 330.14(c)(2)(ii) and (c)(3), respectively, TEA applicants must submit information about 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 OTC active ingredients may submit information on dosage units as the total weight of active ingredient sold and submit information on potential consumer exposure in accordance with the calculations provided in 21 CFR 330.14(c)(2)(ii). Like any applicant submitting a TEA (for a condition not marketed in the United States for more than 5 years), manufacturers or suppliers of OTC active ingredients must also submit a copy of current finished product labeling and provide the information about labeling as listed in 21 CFR 330.14(c)(3) for each country where the condition is marketed.[8] Section IV.I. describes in more detail what product labeling information should be included in the TEA.

G. What is use pattern information and when should I include it in the TEA?

Under 21 CFR 330.14(c)(2)(iv), *use pattern* is defined as how often a drug product is to be used (according to the label) and for how long. Under 21 CFR 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.

H. Should I submit reports from countries regarding adverse drug experiences?

Reports on adverse drug experiences do not need to be submitted with the TEA. However, under 21 CFR 330.14(c)(2)(v), we require the applicant to describe the countries' systems for identifying adverse drug experiences, especially those found in OTC marketing experience. Additionally, the applicant must include in this description how the information is collected, if applicable (21 CFR 330.14(c)(2)(v)). If the condition is subsequently determined to be eligible for inclusion in the OTC drug monograph system, submissions in response to the notice of eligibility must include all serious adverse drug experiences (as defined in 21 CFR 310.305 and 314.80) (21 CFR 330.14(f)(2)).

[8] See 67 FR 3060 at 3064-65.

I. What product labeling information should I include in the TEA?

According to 21 CFR 330.14(c)(3), the applicant must include an English version of the current product labeling from each country in which the condition is 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. We do not expect applicants to submit a copy of every piece of labeling 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 substantially the same on every piece of labeling used in that country. If an applicant does not submit copies of all labeling for a particular country, the TEA should inform the FDA that the labeling that was not submitted for that country is substantially the same as the labeling that was submitted.

J. Am I required to include in the TEA any non-OTC marketing information for currently marketed drug products?

The applicant must include non-OTC marketing information in certain circumstances. TEA regulations (21 CFR 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.

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

There are various sources that may provide information on population demographics that must be included in a TEA under 21 CFR 330.14(c)(2)(iii). The following Web sites are two examples of sources that provide population demographics information:

- The U.S. Central Intelligence Agency World Factbook: https://www.cia.gov/library/publications/the-world-factbook/index.html

- The U.S. Department of State Background Notes: http://www.state.gov/r/pa/ei/bgn/

The national statistical office for a particular country may also provide relevant information. The U.S. Census Bureau International Statistical Agencies Web page lists countries and links to the countries' national statistical offices: http://www.census.gov/aboutus/stat_int.html.
In addition to providing population demographics, under 21 CFR 330.14(c)(2)(iii), the TEA must describe the source(s) from which the population demographic information was compiled.

V. WHAT FORMAT SHOULD I USE IN THE TEA?

A. Information describing the condition

The basic information and detailed description of the ingredient or ingredients required by 21 CFR 330.14(c)(1) can be presented in any format. Although not required, we recommend that applicants include this information at the beginning of the TEA to identify the purpose of the application before providing particular marketing information. We also recommend that the applicant present this information in a table format with any attachments following the table. Table 1 shows an example of how the information can be presented.

Table 1. Basic Information Describing New Condition

Active ingredient or botanical drug substance
Pharmacologic 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 Description
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

If applicants use such a table format, they should separately provide a certificate of authenticity for botanical drug substances, as required under 21 CFR 330.14(c)(1)(ii).

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

Certain information requested for each country must be submitted in a table format (21 CFR 330.14(c)(7)). In addition, we recommend that the applicant include as much of the TEA information as possible in a table with other information as attachments (e.g., labeling). Table 2 is an example of a table that can 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[1,2]
System for identifying adverse drug experiences[1]

[1] Not necessary for conditions that have been marketed OTC in the United States for more than 5 years. See 21 CFR 330.14(c)(8).
[2] Section 330.14(c)(7) states that this information must be included in a table.

Applicants may also summarize some of the marketing experience information in a format that allows easy comparisons among countries. For example, information in Table 2 could be presented in one table providing this information for all of the selected countries (by creating a column for each country).

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

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

You must submit three copies of the TEA to the address provided in 21 CFR 330.14(d). You can also find the address on the Dockets Management Web site at http://www.fda.gov/RegulatoryInformation/Dockets/default.htm.

You may also mail a copy of the TEA directly to the Division of Nonprescription Regulation Development. See the Regulation of Nonprescription Products Web site for mailing addresses: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm093452.htm.

You can mail your TEA copies through the Post Office or by courier (e.g., FedEx or UPS). Identify the submission as a "Confidential Time and Extent Application (TEA)."

Two weeks after submitting your TEA, we recommend that you telephone the Division of Nonprescription Regulation Development to ensure that we have received the TEA. The phone number for the Division of Nonprescription Regulation Development can be found at: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm093452.htm.

B. Is confidentiality protected?

Certain information is considered confidential and is protected to the extent allowed under applicable laws and regulations. Under 21 CFR 330.14(d), all TEAs are handled as confidential upon receipt until such time as a decision is made on the eligibility of the condition. If the condition were found to be eligible for inclusion in the OTC drug monograph system, any information that we deem confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or section 301(j) of the FD&C Act will be removed from the TEA, and the remainder of the application will be placed on public display in the Division of Dockets Management when the notice of eligibility is published (21 CFR 330.14(d)). If the condition is not found to be eligible, the TEA will not be placed on public display, but a letter from the FDA to the applicant stating why the condition was not found to be eligible *will* be placed on public display in the Division of Dockets Management (21 CFR 330.14(d)).

TEA applicants must identify the information, if any, that is considered confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or section 301(j) of the FD&C Act (21 U.S.C. 331(j)) (21 CFR 330.14(d)). Applicants should identify the confidential information in their applications and mark as confidential in the TEA only the pages that they consider to be confidential. The "confidential" stamp mark should be placed at the top or bottom of a page and not stamped directly over submission text. Applicants should mark "confidential" on a page only if there is specific confidential information on that page. Alternatively, applicants can submit two versions of the TEA: (1) a redacted version for public display; and (2) an unredacted version containing all information, including confidential information. The redacted version can summarize marketing information according to continent or region. The unredacted version should contain marketing information for each country.

VII. WHAT HAPPENS AFTER I SUBMIT A TEA?

A. How long does an eligibility determination take, and what happens when eligibility is determined?

After you submit a TEA, we review the TEA to determine whether your condition is eligible to be considered for inclusion in the OTC drug monograph system. We typically make an eligibility determination within 1 year of receiving the TEA.

If we determine that the condition *is not eligible* for inclusion in the OTC drug monograph system, the TEA will not be placed on public display, but a letter from the FDA to the applicant stating why the condition was not found to be eligible *will* be placed on public display in the Division of Dockets Management (21 CFR 330.14(d)).

If we determine that the condition *is eligible* for inclusion in the OTC drug monograph system, the TEA will be placed on public display and a notice of eligibility will be published in the *Federal Register* (21 CFR 330.14(e)). This notice will request that interested persons submit

data that demonstrate general recognition of safety and effectiveness for the condition (21 CFR 330.14(f)).

B. If a condition is found eligible, what information should I provide in response to the notice of eligibility to support my claim that the condition is safe and effective?

Under 21 CFR 330.14(f), submissions in response to a notice of eligibility must include: (1) all data and information listed in 21 CFR 330.10(a)(2) under the outline "OTC Drug Review Information," items III through VII; and (2) all serious adverse drug experiences as defined in 21 CFR 310.305 and 314.80.

Data and information should be presented in a clear and complete manner to facilitate our review. Submitted study reports should include complete descriptions of study methodology. They should not only contain summaries of results but should also include raw data. Inclusion of all cited references (rather than simply including a bibliography) is helpful because we may have difficulty obtaining some references.

C. What types of studies should I submit to support my claim that a condition is safe and effective?

We use the safety, effectiveness, and labeling standards in 21 CFR 330.10(a)(4)(i) through (vi) to evaluate the data submitted to support the safety and effectiveness of a condition (21 CFR 330.14(g)). Accordingly, submitted studies should support safety and effectiveness under those standards.

Data and information that support a finding that a condition is generally recognized as safe "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" (21 CFR 330.10(a)(4)(i)).

Under 21 CFR 330.10(a)(4)(ii), proof of effectiveness ordinarily shall consist of adequate and well-controlled studies as defined in 21 CFR 314.126(b). Five typical features of studies considered to be adequate and well-controlled are that the studies are randomized, are blinded, have sufficient number of subjects, include an appropriate target population, and contain a control arm.[9] The control arm of an adequate and well-controlled trial may use various types of controls, including a placebo, a comparator product, or historical control (21 CFR 314.126(b)(2)).

In addition, only relevant studies should be submitted. An example of a study that we ordinarily would consider irrelevant would be an in vitro effectiveness study when we would require clinical effectiveness studies to approve an NDA for the condition.

[9] See 21 CFR 314.126(b) and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

Other recommended characteristics are formulations similar to U.S. formulations, ideally with multiple formulations studied, appropriate arms to assess each active ingredient independently in combination products, and a use pattern similar to the intended U.S. OTC use pattern. Studies should be conducted according to applicable good laboratory or good clinical practices, as described in 21 CFR parts 58 and 312. In addition, it is useful to provide safety and effectiveness data from other countries as well as any safety and/or effectiveness evaluations from any other regulatory body.

D. Do I need to prepare an environmental assessment with my safety and effectiveness data?

As stated in 21 CFR 25.1, our regulations must be administered in accordance with the policies set forth in the National Environmental Policy Act of 1969 (NEPA). To comply with NEPA, an environmental assessment (EA) of our actions is required unless we determine that a categorical exclusion is warranted (21 CFR 25.20(f) and 25.21).

Most actions on OTC drug monographs have been categorically excluded from the EA requirement under 21 CFR 25.31(a), because the actions generally have not increased the use of active ingredients previously marketed in the United States. However, if we determine that an active ingredient not previously marketed in the United States is GRASE and include it in a monograph, this exclusion from the EA requirement would not apply because our action would increase the use of the active ingredient. Thus, the exclusion under 21 CFR 25.31(a) may not apply to many active ingredients found eligible for inclusion in an OTC drug monograph under the TEA process.

Even when 21 CFR 25.31(a) does not apply, active ingredients found eligible for inclusion in an OTC drug monograph under the TEA process may qualify for the categorical exclusions provided under 21 CFR 25.31(b) or (c). Under 21 CFR 25.31(b), an action on an OTC monograph is excluded from the EA requirement if the action increases the use of an active ingredient, but the estimated concentration of the active ingredient will not exceed 1 part per billion[10] in the aquatic environment. If the action is for an active ingredient that naturally occurs in the environment, 21 CFR 25.31(c) excludes the action from the EA requirement if it does not significantly alter the concentration or distribution of the ingredient, its metabolites, or degradation products in the environment.

To determine whether an action on an OTC monograph meets the requirements for exclusion from the EA requirement under 21 CFR 25.31(b) or (c), we need additional data and information. Therefore, when submitting safety and efficacy data, you should also submit information that will help us make this determination.

To help us determine whether the action meets the requirements for exclusion under 21 CFR 25.31(b), you should submit an estimate of the expected introductory concentration of the eligible active ingredient in the aquatic environment (as described in section III of the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*

[10] 1 microgram per liter

(EA guidance)). If the eligible active ingredient naturally occurs in the environment, we will determine on a case-by-case basis the appropriateness of applying the categorical exclusion under 21 CFR 25.31(c), as described in section III of the EA guidance.

If no categorical exclusion applies to a particular FDA action on a monograph, the preparation of an EA is ordinarily required (21 CFR 25.20). Section IV of the EA guidance explains how to prepare an EA for submission to the FDA.

E. Where do I send my safety and effectiveness data submission?

You can submit your safety and effectiveness data, identified by the docket number, through the following Web site: http://www.regulations.gov. Alternatively, data can be submitted by fax, mail, hand delivery, or courier to the Division of Dockets Management. For contact information for the Division of Dockets Management, see http://www.fda.gov/RegulatoryInformation/Dockets/default.htm.

F. What happens after I submit safety and effectiveness data?

After interested persons have submitted safety and effectiveness data in response to the notice of eligibility, we review the data. We may use an advisory review panel in accord with the provisions in 21 CFR 330.10(a)(3) to evaluate the data, evaluate the data in conjunction with the advisory review panel, or evaluate the data on our own (21 CFR 330.14(g)).

If we make an initial determination that the condition *is GRASE* based on our review of the data, we will propose to include the condition in a monograph, by amending an existing monograph or creating a new monograph if needed (21 CFR 330.14(g)(3)).

If we make an initial determination that the condition *is not GRASE*, we will notify the TEA applicant and other interested persons who submitted data, and publish a notice of proposed rulemaking to include the condition in 21 CFR 310.502 (21 CFR 330.14(g)(4)).

In both cases, TEA applicants and interested persons will have an opportunity to comment on the FDA's initial determination and proposed rule, and to submit additional data (21 CFR 330.14(g)(5)). We will subsequently publish a final rule (or a reproposal if necessary) in the *Federal Register* (21 CFR 330.14(g)(5)).

G. How long does a safety and effectiveness review take?

The TEA route is not an expedited process for revising OTC drug monographs or for getting a particular OTC drug to market. As explained above, after a condition is found eligible for inclusion in the OTC drug monograph system, we evaluate the safety and effectiveness of the condition using the same standards and processes that we use to evaluate any condition under the OTC drug monograph system (21 CFR 330.14(g)). We cannot specify a typical time frame for completion of our evaluation because it is dependent on FDA resources and priorities. In addition, the quality of data submitted to the FDA can affect how long the evaluation takes (see section VII.B.).