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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 330

[Docket No. 96N-0277]

RIN 0910-AA01

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

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

DATES: This final rule is effective February 22, 2002.

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SUPPLEMENTARY INFORMATION: The purpose of this final rule is to establish criteria and procedures by which OTC

conditions may become eligible for consideration in the OTC drug monograph system. Currently, a sponsor wishing to introduce into the United States an OTC drug condition marketed solely in a foreign country must prepare and submit a new drug application (NDA). Likewise, companies with OTC drugs initially marketed in the United States after the 1972 initiation of the OTC drug review must have an NDA. This final rule provides procedures for these NDA drugs to become eligible for inclusion in the OTC drug monograph system by first submitting a time and extent application (TEA) to show marketing "to a material extent" and "for a material time." Once determined eligible, safety and effectiveness data would be submitted and evaluated. This two-step process allows sponsors to demonstrate that eligibility criteria are met before having to expend resources to prepare safety and effectiveness data.

I. Background

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

FDA publishes these conditions in the **Federal Register** in the form of OTC drug monographs, which consist primarily of active ingredients, labeling, and other general requirements. Final monographs for OTC drugs that are GRAS/E and not misbranded are codified in part 330 (21 CFR part 330). Manufacturers desiring to market an OTC drug covered by an OTC drug monograph need not seek FDA clearance before marketing. In a future issue of the **Federal Register**, the agency will be publishing a final call for data for OTC drug products marketed in the United States before May 11, 1972, to be reviewed as part of the original OTC drug review.

In the **Federal Register** of October 3, 1996 (61 FR 51625), FDA published an advance notice of proposed rulemaking (ANPRM) stating that it was considering proposing to amend its regulations to include criteria under which certain

additional OTC drug conditions may become eligible for inclusion in the OTC drug monograph system. Interested persons were invited to submit written comments by January 2, 1997. The agency received 16 comments, which it discussed in section III of a proposed rule that was published in the **Federal Register** of December 20, 1999 (64 FR 71062 at 71067) (the proposed rule).

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

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

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

II. Description of the Proposed Rule

The existing OTC drug regulations in part 330 do not define eligibility requirements for consideration in the OTC drug monograph system or what constitutes marketing to a material

extent or for a material time. The proposed rule and this final rule set forth criteria and procedures for considering additional "conditions" (as discussed in section I of the proposed rule, 64 FR 71062) in the OTC drug monograph system. The definition of "conditions" appears in § 330.14(a) of the final rule.

The proposed rule established procedures for a sponsor with a condition it considered eligible for consideration to provide the agency certain information to establish eligibility. The proposed rule presented these procedures in table 1 format as part of a TEA as follows: (1) Basic chemical information about the ingredient (additional information needed for a botanical ingredient), (2) a list of all countries in which the condition has been marketed, (3) how the condition has been marketed in each country (e.g., OTC general sales direct-to-consumer, sold only in a pharmacy), (4) the number of dosage units sold, (5) marketing exposure (e.g., race, gender, ethnicity), (6) the use pattern in each country, (7) each country's system for identifying adverse drug experiences (ADEs), including method of collection, (8) how long the condition has been marketed in each country, (9) all labeling used during the marketing period in any country, and the time period each labeling was used, (10) all countries where the condition is marketed only as a prescription drug and the reasons why, and (11) all countries where the condition has been withdrawn from marketing or OTC marketing has been denied.

If FDA determined the condition eligible for consideration in the OTC drug monograph system, it would publish a notice of eligibility in the **Federal Register** and place the TEA on public display. The sponsor and other interested parties would then submit data to support safety and effectiveness. If the agency tentatively determined the condition GRAS/E, it would propose to amend the applicable OTC drug monograph or propose a new monograph. There is a comment period for interested persons to comment on the agency's proposal, during which interim marketing would not be permitted. The agency would then publish a final rule, at which time marketing could begin.

Interested persons were invited to submit comments by March 22, 2000. The agency received comments from four industry trade associations, one health coverage association, three suppliers of OTC drug ingredients, and three manufacturers of OTC drug products.

III. Comments on the Proposed Rule

A. General Comments

1. One comment contended that there is no legal basis for the agency's proposal. The comment disagreed with FDA's position that for a drug to qualify for inclusion in the OTC drug review and not be a new drug under section 201(p)(2) of the act the drug must have been used to a material extent or for a material time under its conditions of use in the United States only (64 FR 71062). The comment added that there is no basis in the act to support FDA's interpretation that foreign data cannot be used to satisfy the material time or material extent requirements of the act. The comment noted FDA's willingness in recent years to accept and rely upon foreign data as the basis for approving NDAs for prescription and OTC drugs, food additives, and premarket applications for medical devices.

The agency explained in the proposal (64 FR 71062) that it had previously interpreted the "use" requirements in section 201(p) of the act to mean use in the United States only, and that the proposal represented a change in the agency's interpretation. The agency proposed this change in policy to expand "use" to include foreign marketing experience because it believed certain circumstances of use outside the United States may appropriately be considered to satisfy the use requirements in section 201(p) of the act. The agency considers this approach consistent with its use of foreign data as the basis for approving NDAs for prescription and OTC drugs, food additives, and premarket applications for medical devices. The agency continues to believe that there is an appropriate legal basis for the additional criteria and procedures in this final rule, as described in the proposal.

2. One comment contended that the proposed procedures would effectively terminate the OTC drug monograph process as conceived and implemented to date, noting that the process has included flexibility to consider new conditions and allowed interim marketing for nonmonograph products. The comment added that the agency's procedural regulations for the OTC drug review were designed to be flexible and to establish a standard procedure first for the review of pre-1972 drugs and later to determine the status of post-1972 and foreign marketed drugs. The comment considered the new procedures inflexible and unworkable.

The agency disagrees that the new procedures are inflexible and unworkable and would effectively

terminate the OTC drug monograph process as conceived and implemented to date. The agency also disagrees that the procedural regulations for the OTC drug review were designed for review of post-1972 and foreign marketed drugs. The proposal (37 FR 85, January 5, 1972) and the final rule (37 FR 9464, May 11, 1972) that established the OTC drug review only discussed OTC drugs "now marketed." Estimates of the number of OTC drug products on the market (37 FR 85) only covered the United States. Thus, the original OTC drug review procedures were not developed to address post-1972 and foreign marketed drugs. Accordingly, the agency proposed (64 FR 71062 at 71067) and is modifying the existing procedures in § 330.10 to make them consistent with the new scope of the review. Interim marketing is discussed in comment 21 of section III. D of this document.

3. A number of comments contended that the proposed procedures and data requirements are too complex and protracted, unduly burdensome (more burdensome than the NDA process), unrealistic, prohibitive, and unwieldy to be of practical value to industry. The comments stated that the TEA is too onerous and broad in scope because it requires exhaustive information rather than adequate information to demonstrate marketing history. The comments argued that it is excessive to require exhaustive data from every country in the world for a threshold eligibility consideration. Another comment added that the requirement for a worldwide data search would be a disincentive to companies with good data from a few countries but without the resources to do a worldwide search. One comment added that the safety and effectiveness consideration should be based upon the quality of the data, not upon arbitrarily selected material times, material extents, or listing of countries, and that the scope of certain requirements is quite narrow and restrictive (e.g., show that pharmacy-only sale does not indicate safety concerns). Several comments requested that the procedures be more flexible and less complicated so as to encourage quality products to enter the review process rather than deter them from entry. Other comments suggested that the agency rescind the proposed rule. Two comments recommended that the agency use the same eligibility criteria for foreign ingredients as used for domestic ingredients in the original OTC drug review.

The agency does not consider the TEA too onerous or broad in scope. The TEA is designed to provide FDA basic

information about a condition for which it may have little or no information. The TEA is also designed to provide sufficient information to allow for a one-time assessment of a condition's eligibility for consideration in an OTC drug monograph. The agency agrees with the comments that it is not necessary to require exhaustive data from every country in the world for a threshold eligibility consideration and has modified some of the TEA requirements (see comment 12 of section III.B of this document). The agency agrees that the safety and effectiveness consideration should be based upon the quality of the data. The agency does not believe that the procedures will deter quality products from entering the review process because products with quality data should be able to readily meet the requirements of the process. Excluding prescription-to-OTC switches that the panels could consider, the primary criterion for eligibility in the original OTC drug review was that the ingredient had to be in the U.S. OTC market before May 11, 1972. It would not be practical to use that date for foreign conditions because many conditions that entered the market after that date would be excluded. In addition, none of the foreign conditions have been marketed in the United States and the United States has no experience with these conditions. The agency has developed eligibility criteria, as discussed in the preamble of the proposed rule (64 FR 71062 to 71064), that it considers necessary to provide sufficient information for a condition to be considered for inclusion in the OTC drug monograph system. The agency finds no basis to rescind the proposed rule, and the agency is publishing a final rule so that additional conditions may now begin to be considered.

4. One comment contended that the proposed procedures would establish a nontariff trade barrier in violation of the General Agreement on Tariffs and Trade (GATT). The comment stated that the proposal differentiates between a cosmetic-drug sold in the United States prior to 1972, which is eligible for inclusion in the OTC drug review without any further information, and a cosmetic-drug sold outside the United States prior to 1972, which would be eligible only after submitting a comprehensive TEA. The comment added that the proposal also discriminates against foreign products by prohibiting marketing until publication of a final monograph, while U.S. products may generally be

marketed after publication of a tentative final monograph (TFM).

The issue of a trade barrier in violation of GATT was also raised in the comments on the ANPRM and was discussed in comment 11 of section III.B of the proposed rule (64 FR 71062 at 71072). The agency does not believe that any provisions of this final rule would violate GATT (which is now one of the multilateral agreements annexed to the agreement establishing the World Trade Organization). Among other reasons, foreign-manufactured products marketed in the United States prior to 1972 are treated the same as domestic manufactured products marketed in the United States prior to 1972. Similarly, both foreign and domestic manufactured products marketed in the United States after 1972 under NDAs would be eligible for consideration in the OTC drug review after submission of the same TEAs demonstrating that the same material time and extent criteria have been met. Foreign manufactured products previously marketed only in foreign countries would also be eligible for consideration in the OTC drug review after submission of TEAs that show these same material time and extent criteria have been met. Under this rule, drugs produced in the United States and those produced abroad would be treated the same way, and both would be required to comply with U.S. labeling and manufacturing requirements as a condition of marketing in the United States.

Interim marketing is discussed in comment 21 of section III.D of this document. Under § 330.14(h), products previously marketed only in foreign countries that are included in a tentative final monograph may also, if appropriate, be marketed in the United States before completion of the final monograph.

The provisions of this final rule serve to promote and protect human health and safety and do not create trade barriers.

5. One comment noted that under the proposal a condition is not eligible for OTC drug monograph status if marketing in the United States is limited to prescription drug use only and requested the agency to expand the criteria for monograph status to include drugs marketed by prescription in the United States. The comment contended that FDA may determine drugs to be eligible as GRAS/E for an OTC drug monograph on the basis of various types of evidence, including "significant human experience during marketing." The comment contended that if adequate adverse event information is available for foreign OTC drugs that

remain prescription drugs in the United States, FDA should allow consideration of these active ingredients for possible inclusion in an OTC drug monograph. The comment added that certain prescription conditions were considered for and added to the OTC drug monographs during the original OTC drug review (drugs marketed prior to 1972). Another comment considered the proposal narrow and restrictive because a drug sold OTC in some foreign countries would be ineligible for monograph status if it is marketed by prescription in the United States.

The agency agrees with the comments and believes there was an inconsistency with the criteria proposed in § 330.14(b). Under the proposed criteria, a condition marketed OTC in one or more foreign countries that is limited to prescription use in other foreign countries would be considered for eligibility in the OTC drug monograph system. However, a condition marketed OTC in one or more foreign countries that is limited to prescription drug use in the United States would not be considered for eligibility. The agency has decided to address this inconsistency by removing the criterion in proposed § 330.14(b)(2) to allow conditions marketed OTC in foreign countries that are limited to prescription drug use in the United States to be considered for eligibility in the OTC drug monograph system. If such a condition is found to be eligible, the sponsor must then provide the necessary information, which would include the U.S. prescription marketing experience, as part of the safety and effectiveness submission to establish that the condition is appropriate for OTC status in the United States and that it can be marketed as GRAS/E under the OTC drug monograph system. The agency believes that it can adequately address in its monograph review the issues associated with a product's prescription use in the United States, and the appropriateness of switching the product to OTC use.

6. One comment contended that there is no need for FDA to make a material time/extent determination wholly separate from its consideration of safety and effectiveness.

The agency discussed this subject in comment 13 of section III.C of the proposed rule (64 FR 71062 at 71073) and provided three reasons for the two-step review approach. The comment did not provide any reasoning to support rejecting this approach, and the agency concludes that separate evaluations of material time/extent and safety/effectiveness are the most efficient way to evaluate these additional conditions

for inclusion in an OTC drug monograph.

B. Comments on Criteria for Time and Extent of Marketing

7. One comment contended that the TEA filing reflects a misunderstanding that sponsors must show both material time and material extent. The comment stated that a product is legally required to satisfy the requirement of "to a material extent" or "for a material time," which was intended to satisfy the requirement that a drug be used for sufficient time or have wide enough distribution for discovery of any adverse experiences.

The agency discussed this subject in comment 8 of section III.A of the proposed rule (64 FR 71062 at 71069 to 71070). The agency explained there why a condition that is considered "not a new drug" must satisfy both the material extent and the material time criteria in section 201(p)(2) of the act. The comment did not provide any information to change the agency's position.

8. One comment agreed with most of the proposed time and extent criteria, but contended that specific data on the number of dosage units sold in each country (number of units sold by package sizes, number of doses per package based on labeled directions for use) is difficult to compile, unnecessarily detailed for evaluating time and extent of marketing, and unlikely to be maintained by industry with the degree of specificity proposed in the rule. The comment concluded that specific marketing information related to dosage units should be required only to the extent it is reasonably capable of being compiled. A second comment stated that there should be no numerical floor for the number of units that must have been marketed. Another comment stated that the number of dosage units sold should be replaced by the total quantity of product sold, with an extrapolation to the number of consumer units based on average package size.

The agency has reconsidered how information should be provided on the number of dosage units sold. The agency's primary concern is determining consumer exposure to the condition. The agency has determined that the number of units sold by package sizes (e.g., 24 tablets, 120 milliliters (mL)) and the number of doses per package based on the labeled directions for use may not be necessary to determine a condition's extent of marketing and is removing these requirements from proposed § 330.14(c)(2)(ii). Instead, the agency is

only requiring a list of the various package sizes for each dosage form in which the condition is marketed OTC along with an estimate of the minimum number of potential consumer exposures to the condition using one of the following calculations: (1) Divide the total number of dosage units sold by the number of dosage units in the largest package size marketed, or (2) divide the total weight of the active ingredient sold by the total weight of the active ingredient in the largest package size marketed. Information on package size should be readily available from marketers of the product, if other than the sponsor, or other marketing sources (e.g., wholesalers) and will allow the sponsor to estimate the minimum number of potential consumer exposures to the condition. In addition, to ensure that consumer exposure is adequate for any one dosage form, the agency is changing the proposed criterion in § 330.14(c)(2)(ii) to state "The total number of dosage units sold for each dosage form of the condition." One comment's request for replacing "the number of dosage units sold" with "total quantity of product sold" is discussed in comment 11 of section III.B of this document. The agency agrees that there should be no numerical floor for the number of dosage units that must be marketed and is not including such criteria in this final rule.

9. One comment requested the agency to reconsider its requirement for information regarding geographical and cultural differences (e.g., race, gender, ethnicity) between the countries where the product has been marketed and the U.S. population. The comment contended that this information is difficult to obtain, subjective in nature, and subject to inconsistent evaluation. The comment maintained that specific marketing information related to geographic and cultural distinctions should be required only to the extent it is reasonably capable of being compiled. The comment requested that FDA require this information only in those situations where it is aware of specific cultural and/or geographical differences that would be relevant to the review process. Another comment stated that it should be possible to refer to large geographical areas (e.g., the population of the European Union) to support sufficient variability in terms of culture and gender to show adequate population exposure.

The agency discussed the need for marketing exposure data in comment 11 of section III.B of the proposed rule (64 FR 71062 at 71071 to 71072). Because of the potential breadth of this requirement, the agency is modifying

the criteria in proposed § 330.14(c)(2)(iii) to require, as a means of determining marketing exposure, information on the population demographics (percentages of various racial/ethnic groups) for each country where the condition has been marketed and the source(s) from which this information has been compiled. Examples of sources for this information include the following Internet sites: <http://www.cia.gov/cia/publications/factbook/index.html>, and <http://www.state.gov/www/background/index.html>. The national statistical office for the individual country also may provide relevant information. The agency believes this information will not be difficult to obtain or subjective in nature, and that it can be evaluated consistently. Although sponsors may use the categories and definitions in the Office of Management and Budget's **Federal Register** notice, entitled "Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity," when describing the population demographics of each country, the agency is removing the reference to this document from § 330.14(c)(2)(iii) because other countries may not use all of these categories and definitions.

10. One comment requested that use pattern information (e.g., how often and how long the ingredient is to be used according to its labeling) (proposed § 330.14(c)(2)(iv)) be included as part of the safety evaluation rather than as part of the time and extent information. The comment stated that such information involves an evaluation of historical labeling and appears to be related to safety; thus, it is more appropriate in the safety submission rather than in the TEA.

The agency discussed the need for providing use pattern information as part of the TEA in comment 7 of section III.A of the proposed rule (64 FR 71062 at 71069). The agency stated that this information was needed at that stage of the condition's review to determine if a product's use is different in other countries than it would be in the United States. However, the agency is modifying the criterion in proposed § 330.14(c)(2)(iv) to require use pattern information only when the use pattern varies between countries or when it has changed over time in one or more countries. The agency agrees that use pattern information is also related to the condition's safety, and also may consider it in the safety evaluation.

11. Two suppliers of active ingredients expressed concern about being able to provide accurate information on how their ingredients

are marketed in final form, the number of final product units sold, and the labeling or adverse event reports relevant to finished products. One supplier stated that it could provide information about the countries in which the active ingredients are sold and the quantities sold for OTC use, but that customers would be unlikely to provide their sales data. The comments asked FDA to accept sales and related information from active ingredient manufacturers as evidence of material time and material extent.

The agency has reconsidered the information requirements for a TEA. In addition to the revised requirements discussed in response to other comments, sponsors of TEAs who are manufacturers or suppliers of OTC active ingredients may provide dosage unit information as total weight of active ingredient sold (cumulative total for the specific condition being considered) for each country in which the condition is marketed. This revision to § 330.14(c)(2)(ii) provides active ingredient manufacturers a mechanism to provide pertinent sales data. The agency has also reduced the amount of labeling information that must be provided (see comment 14 of section III.B of this document). The agency discussed the availability of ADE information in the proposal (64 FR 71062 at 71070 to 71071) and the comment did not provide any basis to support changing this requirement.

12. One comment agreed with the importance of the objectives of the data requested in proposed § 330.14(c)(2), i.e., that detailed information from a number of countries addresses some of the ethnic, cultural, and racial variances that may exist among users in foreign markets and the relevance of this information to potential use of the product in the United States. However, the comment considered it burdensome to provide this information from all countries if the product is marketed in a large number of foreign countries. The comment suggested an alternate TEA requirement for products that have 5 years or more of continuous marketing in 50 or more countries and marketing for 20 years or more in one of the "Tier 1" countries for purposes of the export provisions of section 802(b)(1)(A) of the act (21 U.S.C. 382). These countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and the European Union (EU) or a country in the European Economic Area (the countries in the EU and the European Free Trade Association).

The comments suggested that sponsors meeting the threshold criteria would be permitted to select, after

consultation with FDA, six countries that represent both significant markets for the product and cultural diversity. The sponsor would then complete the TEA with information applicable to the six countries or, with FDA's agreement, obtain information by contacting public health officials and otherwise soliciting information on the type of marketing, patterns and conditions of use, and adverse drug experiences from product users in each selected country. The comment concluded that this approach should provide the necessary information for FDA to make its evaluation and provide sponsors the opportunity to consult with the agency to develop reasonable means to collect the information needed to assure FDA of the suitability of foreign-marketed conditions. Another comment stated that the information requested in proposed § 330.14(c)(1), (c)(2)(ii), (c)(2)(iv), and (c)(3) is very difficult, if not impossible, for a manufacturer of the raw material to provide because only the manufacturers of finished products would be able to provide this information. The comment recommended that for classes of OTC drugs for which there are only qualitative instructions for use, such as for sunscreen and antidandruff products, the basic information required would be based on the number of kilograms of the active ingredient sold per year and per country for this intended drug use. In addition, the regulatory status of the ingredient in those countries that have specific legislation controlling the usage of the ingredient, and the maximum amount of the substance allowed to be marketed, would be provided. The comment recommended revisions to § 330.14(c)(1), (c)(2)(ii), (c)(2)(iv), and (c)(3) and the following new § 330.14(c)(2)(vi) to allow certain products to comply with proposed § 330.14(c)(2)(ii):

For sunscreen and antidandruff OTC drugs in which there are no quantitative dosage instructions for the use of the products in the final monographs, list all countries that the drug is approved for use, what maximum concentrations are allowed, any restrictions on usage that are enforced, the number of kilograms sold per country (per year and cumulative), what known adverse effects have been reported and list the other drugs in the same OTC category that it has been combined with. This data to be supplied in tabulated form.

The comment further suggested that these modifications be limited to OTC sunscreen drugs that are permitted for use in annex VII of the EU Cosmetics Directive and the OTC antidandruff

drugs that are regulated as preservation materials in annex VI, or are for restricted use as indicated in annex III of the EU Cosmetics Directive for this purpose. The comment concluded that this approach should assure FDA that the active ingredients in these two classes have had a pedigree of peer review and/or a history of long usage in the EU. Another comment strongly supported annex VII of the EU Cosmetics Directive to demonstrate the safety and effectiveness of four sunscreen agents marketed in Europe.

Another comment contended that it should not be necessary to submit a TEA for an ingredient that has been sold in the United States [under an NDA] for a material time and extent, e.g., including ibuprofen in the internal analgesic monograph. The comment added that under the proposal the only information exempted is labeling from every country.

The agency agrees with the first comment that it may not be necessary to provide detailed information from each country in which a condition is marketed if the condition has extensive marketing in a large number of foreign countries. The agency is providing an alternate TEA requirement if a condition has been marketed OTC in five or more countries with a minimum of 5 continuous years of marketing in at least one country. Sponsors who have this extensive marketing experience for a condition should select at least five of these countries from which to submit information in accord with § 330.14(c)(2)(i) through (c)(2)(iv). Countries that are selected 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 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. This alternate TEA requirement appears in § 330.14(c)(4) of this final rule.

Even though sunscreen and antidandruff products are regulated differently by the EU, both are considered OTC drugs in the United States and are so regulated as part of the OTC drug monograph system. The agency recognizes that it may be difficult for manufacturers of the raw

material to obtain some of the information on finished products. Therefore, the agency is not requiring raw material manufacturers to provide the number of dosage units sold in each country (see comment 11 of section III.B of this document). The total weight of active ingredient sold per country (cumulative) for the intended use of the condition will be adequate, and the agency has revised proposed § 330.14(c)(2)(ii) accordingly in this final rule. The other required information in the comment's proposed § 330.14(c)(2)(vi) is already included in other parts of the regulation. Therefore, the agency sees no need to adopt new § 330.14(c)(2)(vi).

The agency concludes that it is still necessary to submit a TEA for an ingredient already marketed OTC in the United States under an NDA because the agency needs to evaluate if the condition has been marketed to a material extent and for a material time whether the OTC marketing was in the United States or elsewhere. In the proposal (64 FR 71062 at 71081), the agency stated that information on marketing exposure (proposed § 330.14(c)(2)(iii)) and the length of time the condition has been marketed in each country accompanied by all labeling used during the marketing period (proposed § 330.14(c)(3)) need not be provided for OTC drugs that have been marketed for more than 5 years in the United States under an NDA. In this final rule, the agency is removing the requirements to submit certain information if the condition has more than 5 years marketing in the United States under an NDA including: (1) How the condition has been marketed (§ 330.14(c)(2)(i)), (2) a description of each country's system for identifying ADEs (§ 330.14(c)(2)(v)), and (3) all countries where the condition is marketed only as a prescription drug (§ 330.14(c)(5)). The agency is not requiring this information because the information needed to satisfy these requirements is obtainable from the NDA.

13. One comment urged that there not be a rigid and inflexible 5-year marketing requirement to determine material time prior to considering monograph status for an OTC drug active ingredient.

The agency discussed this subject in comment 6 of section III.A of the proposed rule (64 FR 71062 at 71069). The agency noted there that in response to the ANPRM a number of comments agreed with the proposed 5-year minimum requirement to satisfy marketing for a material time. The agency considers a minimum of 5 years

of OTC marketing experience a necessary duration of time to detect infrequent but serious ADEs that are occurring and, thus, provide an appropriate margin of safety. The comment did not provide any information to change the agency's position. However, the agency is modifying the eligibility criteria in proposed § 330.14(b)(3) (new § 330.14(b)(2)) by deleting the word "countries" to clarify that the minimum requirement is 5 continuous years of marketing in the same country. Although the agency recognizes that some conditions may be able to demonstrate marketing to a material extent from marketing in only one country, some conditions may not be able to do so. Therefore, the agency is adding the following sentence to the criteria in new section § 330.14(b)(2): "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."

14. Two comments contended that marketing history (proposed § 330.14(c)(3)) will be difficult to obtain and requested the agency to limit information to a review of time and extent of marketing. One comment requested that specific marketing information related to historical product labeling be required only to the extent it is reasonably capable of being compiled.

The agency has reassessed the historical labeling requirements in proposed § 330.14(c)(3) and determined that the requirements can be modified. Because additional warning and direction information is most likely added over time rather than removed, the agency believes that a condition's current labeling will provide the appropriate, needed information. Therefore, the agency is revising proposed § 330.14(c)(3) to require that sponsors submit a statement of how long the condition has been marketed in each country and how long the current product labeling has been in use. In addition to providing a copy of the current product labeling, the sponsor should state whether that labeling has or has not been authorized, accepted, or approved by a regulatory body in each country where the condition is marketed.

C. Comments on Administrative Procedures

15. Two comments stated that timeframes should be established for publication of proposed and final rules. Based on considerable delays in the rulemaking process, the comments

believed that the delay between publication of a proposed and final rule will not be minimal. Two comments urged the agency to institute specific timeframes for review of TEAs (one comment recommended 90 days) and safety and effectiveness submissions. The comments stated that the OTC drug review was implemented in 1972, and has yet to be completed and that some foreign ingredient petitions have languished before the agency for years. One comment expressed concern that submissions would continue to languish without specific review timeframes. The comment cited the agency's rationale in the proposed rule for not including review timeframes. The comment argued that it is the applicant's responsibility to ensure that submissions are prepared adequately and that it is unlikely that the agency will be overrun with applications upon implementation of the final rule. The comment stated that review timeframes would be in keeping with the goal of the Food and Drug Administration Modernization Act (FDAMA) to improve the efficiency of application review and that the agency has a public health obligation to ensure that applications are reviewed in a timely manner. The comments concluded that it is critical that timeframes be established if the agency does not permit interim marketing.

The agency agrees that TEAs and safety and effectiveness submissions should be reviewed in a timely manner consistent with the goal of improved efficiency. The Division of OTC Drug Products will be responsible for evaluating all TEAs and overseeing the progress of safety and effectiveness reviews. As differences will invariably occur in the quantity and quality of the TEA and GRAS/E submissions received, it is not possible to set exact timeframes for completing these reviews. The Division will strive to complete TEA evaluations within 90 to 180 days of receipt and will implement procedures to ensure that agency resources are used appropriately and result in timely action on safety and effectiveness submissions. The Division will contact the sponsor within 180 days about the status of its request.

The anticipated workload for reviewing these additional conditions is difficult to predict. The agency estimated in the proposal (64 FR 71062 at 71078 to 71079) and in this final rule that the number of TEAs submitted annually would be 50, with 30 approved, and with 3 subsequent safety and effectiveness submissions for each approved TEA. The agency received only one comment on these estimates to

help with its workload projections. That comment stated that it is unlikely that the agency will be overrun with applications upon implementation of the final rule. The agency notes that another comment from a foreign industry association representing the cosmetics, toiletries, perfumes, and detergent industry stated that it represented 350 member companies who produce cosmetic products for markets all over the world and that it has been waiting for this new process for a long time (Ref. 1). If a number of this association's members sponsor TEAs, the agency's workload estimates could be low. The agency predicts that as it gains experience with evaluating the foreign data, the speed of its reviews should increase. While the agency is currently unable to project the timeframe it will take to publish proposed rules, it anticipates that the time between proposed and final rules should be short, in many cases because the proposed action will be to add another ingredient to an already existing monograph for which the basic OTC labeling for the product is already established. When a new monograph and OTC drug product labeling is initially established, the agency anticipates that the timeframe between proposed and final rules may be somewhat longer.

16. One comment offered suggestions for streamlining the review process for TEAs and safety and effectiveness submissions. For TEAs, the comment suggested that the agency publish a guidance document to help ensure that the content and format of applications are submitted in a uniform matter. The comment stated that the agency could then use the refuse-to-file concept for applications that do not meet the basic requirements. For safety and effectiveness submissions, the comment fully supported voluntary use of accredited outside organizations or individuals, such as a third-party review program developed by the European Sunscreen Manufacturers Association (Ref. 2) or FDA's medical devices pilot program for third-party review of selected premarket notifications. The comment believed that the agency could implement such a program under the authority of FDAMA. Another comment also strongly supported third party review to reduce review time.

The agency may publish a guidance document to assist manufacturers to organize TEAs in a uniform manner. However, the agency did not want to delay publication of this final rule while developing that guidance document. In the meantime, sponsors should organize their TEA in the sequence in which

information is listed in § 330.14(c). The agency will not use a "refuse-to-file" concept (a threshold determination) for TEAs that do not meet the basic requirements. The agency will do a substantive review of all TEAs, and any TEA that does not contain the required information will result in the condition being found not eligible for consideration.

The agency used a third party review system (advisory review panels) for the original OTC drug review and states that it may use an advisory review panel in § 330.14(g) of the new procedures. When a third-party reviews the safety and effectiveness data, the agency still needs to do its own independent evaluation of the data. Therefore, in the new procedures in § 330.14(g), the agency states that it may evaluate the data in conjunction with the advisory review panel or on its own without using an advisory review panel. Both of these procedures are intended to reduce the overall review time. Based on the number of conditions submitted for review, the agency may consider other alternatives, as necessary, to review submissions in a timely manner.

17. Two comments requested confirmation that the agency would maintain the confidentiality of ineligible TEAs. One comment recommended that this information be returned to the applicant. The comments also requested confirmation that sales data identified by the company in an eligible TEA as trade secret or confidential would remain confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or section 301(j) of the act (21 U.S.C. 331(j)). One comment stated that it is unclear whether the agency intends to notify the applicant if it does not agree with the request for confidential treatment. The comment requested that the agency clarify that it will give notice, consistent with 5 U.S.C. 552(b), so that applicants can determine whether to withdraw the information.

The procedures related to the confidentiality of a TEA are in § 330.14(d). FDA processes a TEA as confidential until a decision is made on the eligibility of the submitted condition for consideration in the OTC drug monograph system. If the condition is not found eligible, the agency will not place the TEA on public display. Only a letter from the agency to the applicant, stating why the condition was not found acceptable, will be placed on public display in the Dockets Management Branch. However, the agency cannot return the TEA to the applicant, but must retain it as the data upon which the agency made its decision.

If the condition is found eligible, the agency will place the TEA on public display after deletion of any information deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). This is similar to the process used for submissions to the advisory review panels under § 330.10(a)(2) of the OTC drug review administrative procedures. Under those procedures, when the agency published a panel's report (ANPRM) in the **Federal Register**, it stated in the notice that all of the information that had been submitted to the panel would be put on public display 30 days after the date of publication except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or 21 U.S.C. 331(j). (Section 330.10(a)(2) has been updated to also include 5 U.S.C. 552(b).) None of the information submitted to the panels was specifically designated as confidential. Requests for confidentiality were to be submitted to the agency during that 30-day period for the agency to evaluate before placing the submissions on public display. Under the new procedures in § 330.14(d), a sponsor must identify what information in the TEA it considers confidential under the above statutory provisions. The agency's general philosophy is that most, if not all of the information in a TEA should be considered public information. As discussed below, the agency has revised the information requirements to take this into account.

The agency has determined that most of the required information would not be considered confidential in making an eligibility determination. Total sales figures covering a period of years historically have not been considered confidential in the OTC drug review process. The agency has determined that yearly sales figures do not need to be provided and has revised proposed § 330.14(c)(2)(ii) accordingly in this final rule. However, if a sponsor needs to provide yearly sales figures to explain something about the marketing of a condition, it should do so but should not expect the agency to keep the information confidential.

Section 330.10(a)(2) only requires a sponsor to provide a statement of the quantities of active ingredients of the drug product. It does not require inactive ingredient information and that information should not be provided unless it appears in the product's labeling. Information about a color or fragrance in the product is not required and should not be included in the TEA. Information about inactive ingredients generally is not considered confidential, because such information would appear

in the labeling of the OTC drug or drug-cosmetic product in the United States. If a specific manufacturing process is included in a TEA because that information is necessary to explain the product and that process relates to the "product" and not the "active ingredient(s)," it may be considered confidential, unless it has a bearing on the product's safety and effectiveness. Other than this limited situation, the agency does not anticipate that other information in a TEA will be considered confidential. The agency's view is that consideration for OTC drug monograph status is a public process and all information provided should be part of the public record if the condition is determined to be eligible. If the agency does not agree with a sponsor's request for confidential treatment of specific parts of a TEA, it intends to discuss the matter with the sponsor before placing the TEA on public display, just as it did with parts of the submissions made to the panels under the original OTC drug review.

18. One comment recommended that any advisory committees used to make GRAS/E determinations for foreign marketed products be comprised of experts with OTC drug experience, including experience outside of the United States. The comment stated that this is necessary to properly assess and appreciate the full implications of non-U.S. marketing and regulatory systems under which these ingredients may have been marketed.

The agency intends to use its Nonprescription Drugs Advisory Committee (NDAC) as the primary advisory committee to consider GRAS/E determinations for foreign marketed products. NDAC will be supplemented by members from other committees as applicable to the subject matter being considered. These committee members will have OTC drug experience, some of which may include experience outside of the United States, depending on the composition of the agency's advisory committees, which changes yearly. The agency intends to allow sponsors to present information to inform advisory committees that consider GRAS/E determinations for foreign marketed products about the regulatory systems under which these ingredients may have been marketed.

19. One comment recommended that sponsors be tentatively notified if the condition can not be GRAS/E and be provided an opportunity to supplement their submission or withdraw it, rather than receiving notification from the agency that the condition is not GRAS/E. The comment explained that a determination of not GRAS/E may be

inconsistent with the condition's regulatory status in other countries, and the sponsor should have the opportunity to withdraw the submission prior to a final agency decision.

The agency intends to use its established OTC drug review feedback procedures to notify sponsors and other interested parties who have submitted data and information in response to a notice of eligibility if a condition has been determined not to be GRAS/E. Parties can respond to a feedback letter and supplement their submissions. The agency may request a response within a specified timeframe in order to complete its review in a timely manner. A sponsor can also withdraw its request for the agency to consider its submission (which would not stop the agency from publishing its decision in the **Federal Register**), but the submission is part of a public docket and will not be returned. Parties will have another opportunity to respond when the agency publishes a notice of proposed rulemaking to include the condition in § 310.502 (21 CFR 310.502). (See § 330.14(g)(4) and (g)(5).)

20. One comment requested that the agency begin to accept TEAs pending the completion of the final rule. The comment based this request on the delay in issuing the final rule and numerous citizen petitions pending before the agency. The comment stated that such actions would be consistent with notifications for Generally Recognized as Safe (GRAS) status for food substances under the agency's proposed rule for GRAS notifications. The comment also requested that the agency equitably resolve its back log of citizen petitions by giving priority to those petitions which have been pending for more than 10 years.

The agency decided not to accept TEAs prior to completion of the final rule so that all TEAs that are submitted will be in the format required by this final rule. Likewise, the agency will be responding to the pending citizen petitions (for considering certain foreign conditions for OTC drug monographs) by telling the petitioners to submit TEAs with the required information in the proper format. A petitioner should be able to readily convert their petition to a TEA and submit it to the agency to begin the review process. TEAs will generally be reviewed in the order they are received. However, if the petitioners convert their pending citizen petitions to TEAs and submit them within 120 days of the publication date of this final rule, the agency will give these TEAs priority review.

D. Comments on Marketing Policy

21. A number of comments disagreed with the agency's proposed marketing policy. The comments requested that the agency allow interim marketing at different times: (1) Once the condition has been determined eligible for consideration, or (2) once the condition has been proposed in the **Federal Register** as GRAS/E and a United States Pharmacopeia (USP) monograph is in place. The comments stated that interim marketing has existed for U.S. marketed products under the OTC drug review, there is precedent for extension of the practice under the new criteria, and most conditions submitted for consideration will pose no greater risk than category III ingredients currently marketed or marketed over the last 25 years. The comments stated the principles of administrative law require the agency to apply practices consistently between similar products with similar circumstances. One comment concluded that, at a minimum, the agency should consider requests for interim marketing as part of the TEA and approve such marketing on a case-by-case basis. Another comment added that there is a need for access to a broader range of safe and effective OTC sunscreen ingredients and the agency should distinguish these ingredients. The comment believed interim marketing for sunscreens and other topical products should be available if the condition has been cleared for safety by an appropriate foreign governmental body such as the Scientific Committee on Cosmetics and Non-Food Products (SCCNFP) in Europe.

One comment believed that the prohibition against interim marketing would inappropriately bar the marketing of a product that is not a "new drug" and would be inconsistent with the agency's current enforcement policy regarding interim marketing of products currently under consideration in the OTC drug monograph system. Two comments claimed that a condition marketed after it has been proposed in **Federal Register** as GRAS/E does not constitute a "new drug" under the statutory definition. One comment maintained that a condition is legally no longer a new drug once it has been found to be GRAS/E and been determined to be marketed to a material extent and for a material time. The comments stated that there is no statutory authority for the agency to prevent the marketing of a product that is not a new drug, and that the agency has no legal basis for taking enforcement action against the marketing of such

products. The comment concluded that once a proposed monograph amendment is published in the **Federal Register**, there is no sound policy basis for permitting the marketing of conditions with U.S. marketing history and not permitting marketing of conditions with foreign marketing history.

Other comments contended it was not necessary to only allow marketing under final OTC drug monographs. One comment contended that it is not clear whether foreign marketed OTC products would present any greater risk than domestic products at the same stage of review. The comment added that to prohibit interim marketing implies that public comment on safety and effectiveness is required to validate the agency's conclusions. The comment maintained that this position is inconsistent with the agency's expert role of safeguarding the public health. Two comments disagreed that marketing only under a final OTC drug monograph would allow for a thorough public consideration of any safety and effectiveness issues that might arise before marketing begins. One comment stated that the examples given by the agency of topically applied ingredients with prior safety concerns was not persuasive. The comment noted that the safety concerns were not so significant as to prevent OTC marketing of those ingredients under less stringent criteria than currently proposed.

One comment believed that requiring completion of a USP monograph should not be a reason to limit marketing to only under a final monograph. The comment acknowledged the importance of establishing USP monograph standards for OTC drug active ingredients, but objected to the requirement since the agency has not required USP monographs prior to the marketing of active ingredients already under consideration in the OTC drug review.

Two comments disagreed with the agency's statement that marketing only under a final OTC drug monograph would allow manufacturers to avoid expensive relabeling when changes occur between the proposal and the final rule. One comment argued that it is not FDA's place to make business decisions for industry, which might in fact conclude that the marketing potential of the product is worth the risk. The comment added that all manufacturers of OTC drug products that are not yet subject to a final monograph face the same risk. The comments concluded that it should be left up to OTC manufacturers to determine whether the revenue and

product recognition lost from any proposed restrictions on interim marketing would outweigh any potential costs of relabeling.

The agency agrees that the interim marketing policy should be consistent between similar marketed products. Conditions that were reviewed by the OTC advisory review panels were allowed to be marketed during the course of the review if they had been marketed OTC in the United States when the review began. Conditions that were not marketed OTC in the United States when the review began could not be marketed until a panel's report was published in the **Federal Register** and the agency did not disagree with the panel's recommendations (see 21 CFR 330.13). When a new condition was submitted for consideration after a panel's report was published and before a TFM was published, the agency usually addressed the status of that condition in the TFM. The agency stated in the TFM that marketing may begin with publication of the TFM or not until public comments were received on the TFM and a notice of enforcement policy was published in the **Federal Register** allowing marketing to begin. A similar procedure was used if a new condition was proposed for inclusion in a monograph after the TFM was published but before a final monograph was issued. Interim marketing was usually allowed because of the period of time projected before the final rule would issue.

For those OTC drug monographs that are not final yet and where finalization is not imminent, after the agency has evaluated the comments to a proposed rule to include a new condition in a TFM as GRAS/E and the agency has not changed its position as a result of the comments, the agency will then publish a notice of enforcement policy to allow interim marketing. This enforcement notice will be similar to those used in the original OTC drug review and will allow 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. However, interim marketing will not be allowed if USP-NF compendial monograph standards for the condition do not exist.

For those conditions proposed to be included in a final OTC drug monograph or where a monograph for the condition does not exist and a new monograph is being proposed, interim marketing will not be allowed. It will first be necessary to seek public comment on the amendment to a final

monograph or whether a new monograph should be established. The agency will not issue an enforcement notice under these circumstances because it takes the same amount of time and agency resources to resolve any outstanding issues and to proceed directly to issuance of a final rule.

22. One comment expressed concern that the proposed eligibility criteria would require the submission of an NDA or TEA for even a slight variation of a monograph product. The comment cited examples that could trigger the requirement of an NDA or TEA, such as a simple combination of two well established OTC drug ingredients or immaterial changes in dosage form or concentration. The comment argued that a condition not authorized by a final monograph is not automatically a "new drug" and the agency has the discretion under 21 CFR 310.3(h), to recognize that not all new conditions make a product "new." The comment concluded that the agency should reaffirm its authority to authorize interim marketing for both pre-1972 and post-1972 non-monograph conditions, consistent with its practice of issuing notices of enforcement policy for products that are the same as monograph products but for immaterial changes in such characteristics as dosage form or concentration.

Variations from a monograph product or a condition being considered may or may not trigger the need for a TEA or NDA. A combination of two well established OTC drug ingredients that is not included in an existing OTC drug monograph or that has not been marketed in the United States would need a TEA. If one of the ingredients is marketed under an NDA, the product is considered a new drug and the combination would need an NDA. A TEA could be submitted for a change in concentration outside that included in an existing OTC drug monograph if that concentration has foreign marketing experience that meet the eligibility criteria. Information would be needed to support the safety and benefit of a higher concentration (as occurred with hydrocortisone for external analgesic use in the original OTC drug review) or the effectiveness of a lower concentration. If a condition marketed in one foreign country at one concentration is found eligible to be reviewed, another sponsor using a different concentration in another country may wish to submit a TEA and request that both concentrations be evaluated simultaneously.

Most OTC drug monographs for oral products are not dosage form specific. Most OTC drug monographs for topical products also are not dosage form

specific and may state that the product is in a dosage form such as a cream, gel, lotion, or ointment. Some OTC drug monographs for topical products are dosage form specific and state that particular ingredients must be in a specific vehicle, e.g., in a suitable water soluble or oleaginous ointment base. Even this specific requirement would allow some flexibility for minor changes in the dosage form. Depending on the OTC drug monograph involved, any interim marketing policy for additional conditions in § 330.14(h), will address the dosage form concentration, and other information of the condition being allowed interim marketing status.

E. Comments on Safety and Effectiveness

23. One comment believed that the absence of adverse experience reporting systems in foreign countries for either drugs or cosmetics should not preclude a condition from being considered GRAS/E. The comment added that there is nothing in the act or FDA regulations that makes the absence of such information determinative of a condition's status.

The agency agrees that the absence of an adverse experience reporting system in a foreign country for drugs or cosmetics does not necessarily mean that a condition cannot be GRAS/E. The GRAS/E determination will be based on the overall quality of the data and information presented to substantiate safety and effectiveness.

F. Comments on Specific Active Ingredients

24. One comment requested that the agency reverse the category II status of the sunscreen ingredient 3-(4-methylbenzylidene)-camphor (Eusolex 6300) and permit its marketing upon publication of the final rule. The comment based this request upon its updated citizen petition that addresses the eligibility criteria in the proposed rule and an established USP monograph for 3-(4-methylbenzylidene)-camphor. The comment asserted that the agency's decision to place Eusolex 6300 in category II and the subsequent 20 year delay in addressing the foreign marketing data in their citizen petition raise serious legal concerns under section 10 of the Administrative Procedure Act.

This comment is not directly related to this final rule. The agency discussed the status of this ingredient and its pending citizen petition in both the TMF (58 FR 28194 at 28210 to 28211, May 12, 1993) and the final monograph (64 FR 27666 at 27669 to 27670, May 21, 1999) for OTC sunscreen drug products,

stating that a decision was needed on the use of foreign marketing data before this ingredient would be considered for inclusion in that monograph. With publication of this final rule, the sponsor may now submit a TEA for FDA to determine whether the condition is eligible for consideration in the OTC drug monograph system.

IV. Legal Authority

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

(1) Any drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, * * * or (2) Any drug * * * the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions. To market a new drug, an NDA must be submitted to, and approved by, FDA before marketing. Only drugs that are not new drugs may be covered by an OTC drug monograph. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act. FDA's regulations under part 330 outline the requirements for OTC human drugs that are GRAS/E and not misbranded. New § 330.14 adds additional requirements.

V. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104-121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; and distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a

substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure of \$100 million (adjusted annually for inflation) in any one year by State, local, and tribal governments, in the aggregate, or by the private sector.

The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive order. Office of Management and Budget (OMB) has determined that this final rule is a significant regulatory action as defined by the Executive order and so is subject to review. Although the agency does not believe that this rule will have a significant economic impact on a substantial number of small entities, there is some uncertainty with respect to the estimated future impact. Thus, a regulatory flexibility analysis is presented below.

A. Regulatory Benefits

The purpose of this final rule is to establish criteria and procedures by which OTC conditions may become eligible for consideration in the OTC drug monograph system. Currently, a sponsor wishing to introduce into the United States an OTC drug condition marketed solely in a foreign country must prepare and submit an NDA. Likewise, companies with OTC drugs initially marketed in the United States after the 1972 initiation of the OTC drug review must have an NDA. This final rule provides procedures for these NDA drugs to become eligible for inclusion in the OTC drug monograph system by first submitting a TEA to show marketing "to a material extent" and "for a material time." Once determined eligible, safety and effectiveness data would be submitted and evaluated. This two-step process allows sponsors to demonstrate that eligibility criteria are met before having to expend resources to prepare safety and effectiveness data.

The flexibility to market drug products under FDA's OTC drug monograph system provides an overall net benefit to the companies seeking to use this approach, as well as to the American public. One important benefit to sponsoring companies is the saving of NDA user fees. The Prescription Drug User Fee Act (21 U.S.C. 379h) requires a one-time application fee for each NDA submitted, and yearly product and establishment fees, as applicable, for each NDA approved. For FY 2000, these

fees are \$285,740 (applications with clinical data), \$19,959, and \$141,971, respectively. Therefore, one-time user fees of \$285,740, and ongoing fees of up to \$161,930 (\$19,959 + \$141,971) are avoided if the company can establish that the condition should be included in an OTC drug monograph.

Also, most manufacturers would experience a paperwork savings when seeking OTC drug monograph status instead of an NDA. For example, in most instances, the manufacturing controls information needed for submitting an NDA is not required for a monograph submission. Ongoing reporting requirements associated with periodic and annual reports are also avoided. Based on previous estimates of the paperwork hours needed to comply with these requirements and assuming a 33 percent reduction in paperwork activities, FDA estimates that eliminating manufacturing controls information from an application would bring a one-time savings of approximately 530 hours and an annual savings of 40 hours per submission. Applying the 1999 labor rate of \$33.95 per hour for an industrial engineer (Ref. 3) (with a 40 percent adjustment for benefits), these one-time savings are approximately \$17,994 (530 x \$33.95/hour) per submission. Likewise, using the 1999 professional and managerial labor rate of \$27.90 per hour (Ref. 3) (including a 40 percent benefit rate), the ongoing savings from the elimination of periodic and annual reports would equal approximately \$1,116 (40 x \$27.90/hour) per product.

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

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

B. Regulatory Costs

FDA estimates that the information needed for a TEA to meet the eligibility criteria for "material time" and "material extent" would take firms approximately 480 hours to prepare. Using the 1999 professional and managerial labor rate of \$27.90 per hour (Ref. 3) (including a 40 percent benefit rate), this cost amounts to approximately \$13,392 (480 hours x \$27.90/hour) per submission. The costs associated with requiring publication in an official compendium, where applicable, would be minimal as similar information is often prepared for publication in a foreign pharmacopeia and most companies already have such standards as part of their manufacturing quality control procedures.

Considering the potential one-time cost savings described above of \$303,734 (\$285,740 + \$17,994) associated with prescription drug user fees and reduced reporting requirements, FDA calculates a one-time net cost savings to industry of up to \$290,342 (\$303,734 - \$13,392) per submission. Future yearly cost savings could total \$21,075 (\$19,959 + \$1,116) per product and \$141,971 per establishment if this were the establishment's only product. Accordingly, FDA estimates that if it receives 25 to 50 TEA submissions a year, the industry would save between \$7.3 million and \$14.5 million in one-time costs alone. The agency notes, however, that companies would submit conditions for OTC drug monograph status only where it would be profitable for them to do so.

Since 1991, the agency has approved six requests for the inclusion of post-1972 U.S. OTC drug conditions in a monograph. Four of these requests consisted of a previously unapproved concentration, dosage form, dual claim, and product combination without OTC marketing experience. Similar conditions are not allowed under the final rule without a minimum of 5 continuous years of adequate OTC marketing experience. These manufacturers would need to either market their product under an application for 5 years in the United States or have 5 years of sufficient marketing experience abroad to qualify for inclusion in a monograph. Accordingly, this rule could result in lost sales dollars for those few future applicants who, in the absence of this rule, might have successfully petitioned FDA to have a product with less than 5 years marketing experience included in a monograph. Likewise, other manufacturers would have to wait until

either the agency includes the condition in a final monograph publication, or the agency evaluates the comments to a proposed rule to include a new condition in a TFM GRAS/E and then publishes a notice of enforcement policy allowing interim marketing, before they could market the product or a product variation without an application. Due to the limited number of requests approved to date, it is unlikely that many manufacturers will be significantly affected by these requirements.

C. Small Business Analysis

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

1. Description and Objective of the Final Rule

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

2. Description and Estimate of the Number of Small Entities

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

preparation manufacturing firms are small entities.

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

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

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

4. Identification of Federal Rules that Duplicate, Overlap, or Conflict With the Final Rule

The agency is not aware of any relevant Federal rules that may duplicate, overlap, or conflict with the final rule.

5. Impact on Small Entities

As described above, some manufacturers could be adversely affected by the 5-year material extent and material time requirements, causing a loss in future sales dollars. The agency cannot quantify this impact. However, based on the limited number of post-1972 conditions approved to date that would not have met the 5-year material extent and material time requirements, FDA believes that few manufacturers will be significantly affected.

6. Analysis of Alternatives

In developing the requirements of this rule, the agency considered two alternatives. Initially, FDA contemplated a one-step evaluation process, where sponsors would submit safety and effectiveness data concurrently with their TEA. However, the agency decided that this process would be less efficient because it would require sponsoring companies to expend resources to prepare safety and effectiveness data before the agency

determines whether eligibility criteria have been met.

The agency also considered allowing manufacturers of post-1972 U.S. OTC drugs to market prior to inclusion in a final OTC drug monograph, as long as the agency had tentatively determined that the condition is GRAS/E. However, to allow for thorough public consideration of any safety and effectiveness issues that might arise before broad marketing of the condition begins under the OTC drug monograph system, the agency proposed that interim marketing should not be allowed under the OTC drug monograph system either for post-1972 U.S. conditions or for conditions with no previous U.S. marketing experience. Under this final rule, the agency has determined for those OTC drug monographs that are not final yet and where finalization is not imminent, after the agency has evaluated the comments to a proposed rule to include a new condition in a TFM as GRAS/E and the agency has not changed its position as a result of the comments, that it will then publish a notice of enforcement policy to allow interim marketing. This enforcement notice will be similar to those used in the original OTC drug review and will allow 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. Interim marketing under these circumstances will also be dependent upon completion of official USP-NF monograph standards, as discussed above. For those conditions proposed to be included in a final OTC drug monograph or where a monograph for the condition does not exist and a new monograph is being proposed, interim marketing will not be allowed. Under these circumstances, the agency expects that it would take the same amount of time to include the condition in a final monograph as it would to publish an enforcement notice.

7. Response to Comments

In response to public comment, the agency simplified the TEA criteria and decided to publish an enforcement notice to permit interim marketing when the finalization of the OTC drug monograph is not imminent, after the agency has evaluated the comments to a proposed rule to include a new condition in a TFM and the agency has not changed its position as a result of the comments. Several comments stated that the TEA is unduly burdensome because the required information is both unnecessarily detailed and difficult to

compile. The final rule modifies how information should be provided on the number of dosage units sold, clarifies the criteria for determining marketing exposure, and revises the historical labeling requirements. These changes will further define the information that is necessary for the agency to determine whether the condition has been marketed to a material extent and for a material time. The agency still estimates that it will take 480 hours to prepare a TEA.

A number of comments disagreed with the proposed interim marketing policy. The comments asserted that interim marketing should be allowed, and that it should be left up to individual OTC manufacturers to determine whether the revenue and product recognition lost from the proposed restrictions on interim marketing would outweigh any potential costs of relabeling resulting from the final monograph. Therefore, for those OTC drug monographs that are not final yet and where finalization is not imminent, after the agency has evaluated the comments to a proposed rule to include a new condition in a TFM as GRAS/E, and the agency has not changed its position as a result of the comments, the agency will publish a notice of enforcement policy to allow interim marketing. This notice will allow 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. Thus, in these cases, manufacturers can assess revenues and projected costs versus potential costs if relabeling, recall, or other regulatory action results from the final monograph. For those conditions proposed to be included in a final OTC drug monograph or where a monograph for the condition does not exist and a new monograph is being proposed, interim marketing still will not be allowed. However, under these circumstances, the agency expects that it would take the same amount of time to include the condition in a final monograph as it would to publish an enforcement notice. Therefore, OTC manufacturers should be able to begin marketing their product under a final rule in the same amount of time that they would have had to wait for the agency to issue an enforcement notice.

Under the Unfunded Mandates Reform Act, FDA is not required to prepare a statement of costs and benefits for this final rule because this final rule is not expected to result in any 1-year

expenditure that would exceed \$100 million adjusted for inflation.

This analysis shows that the agency has considered the burden to small entities. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Paperwork Reduction Act of 1995

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

In the proposal, FDA invited comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including the use of automated collection techniques, when appropriate, and other forms of information technology. The agency did not receive any specific comments on these items.

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

Description: FDA is finalizing additional criteria and procedures by which OTC conditions may become

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

FDA received no comments on the Paperwork Reduction Act section of the proposed rule. However, OMB has requested, in its review of FDA's request for approval of the proposed information collection resulting from this rulemaking, that FDA look into the possibility of applying electronic collection techniques to this collection. There is no requirement in this rulemaking that sponsors submit TEAs electronically. However, the Center for Drug Evaluation and Research has issued the following guidances to facilitate the electronic submission of marketing applications: "Guidance for Industry: Providing Regulatory Submissions in Electronic Format—General Considerations" and "Guidance for Industry: Providing Regulatory Submissions in Electronic Format—NDA's." These guidances were issued in January 1999 and are available at <http://www.fda.gov/cder/guidance/index.htm>. Also available at this Internet site is a document entitled "Example of an Electronic New Drug Application Submission." These guidances provide recommendations for submitting electronic submissions in the appropriate format. Sponsors should refer to the formatting recommendations in these guidances if they wish to submit a TEA electronically.

Concerning the electronic submission of information to the Dockets Management Branch, over the last several months the Dockets Management Branch has been accepting comments electronically on specific dockets as part of a pilot program. An Internet address and an e-mail address have been set up to accept these comments. Parties may submit comments to the Dockets Management Branch through the Internet or e-mail at: <http://www.fda.gov/ohrms/dockets/default.htm>. Parties should then select "submit electronic comments" and follow the directions. Over the next several years, FDA expects to be able to accept electronic submissions of TEAs and safety and effectiveness data, which would eliminate the need for multiple paper copies.

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

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

One amendment revises items IV.A.3, IV.B.3, IV.C.3, V.A.3, V.B.3, and V.C.3 of the "OTC Drug Review Information" format and content requirements to add the words "Identify common or frequently reported side effects" after "documented case reports." This revision clarifies current requirements for submitting documented case reports and only requires sponsors to ensure that side-effects information is identified in each submission. FDA estimates that it will take sponsors approximately 1 hour to comply with this requirement.

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

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

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

Under § 330.14(f)(2), sponsors are required to include in each safety and effectiveness submission all serious

ADEs from each country where the condition has been or is currently marketed as a prescription or OTC drug product. Sponsors will be required to provide individual ADE reports along with a detailed summary of all serious ADEs and expected or frequently reported side effects for the condition. FDA believes that the burden associated with this requirement will be minimal because individual ADE reports are already required as part of the "documented case reports" in the "OTC Drug Review Information" under § 330.10(a)(2). FDA estimates that the time required for preparing and

submitting a detailed summary of all serious ADEs and expected or frequently reported side effects will be approximately 2 hours.

Due to the anticipated number of foreign conditions likely to seek immediate consideration in the OTC drug monograph system, the annual reporting burden estimated in table 1 below is the annual reporting for the first 3 years following publication of the final rule. FDA anticipates a reduced burden after this time period.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
330.10(a)(2) (safety and effectiveness submission)	93	1	93	800	74,400
330.14(c) (time and extent application)	25	2	50	480	24,000
330.14(f)(2) (adverse drug experience reports)	90	1	90	2	180
Total					98,580

The information collection provisions of the final rule have been submitted to OMB for review. Prior to the effective date of the final rule, FDA will publish a document in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in the final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. References

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

1. Comment No. C20, Docket No. 96N-0277, Dockets Management Branch.
2. Comment No. C24, Docket No. 96N-0277, Dockets Management Branch.
3. "1999 Occupational Earnings Data," U.S. Department of Labor, Bureau of Labor Statistics, ftp://ftp.bls.gov/pub/special.requests/lf/att39.txt, April 26, 2000.
4. U.S. Department of Commerce, Economics and Statistics Administration, Bureau of the Census, "Industry Series Drugs," 1992 Census of Manufactures, Table 4, p. 28C-12.

List of Subjects in 21 CFR Part 330

Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner

of Food and Drugs, 21 CFR part 330 is amended as follows:

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

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

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

2. Section 330.10 is amended as follows:

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

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

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

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

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

f. In paragraphs (a)(6)(i) and (a)(9) by removing the word "is" and adding in

its place the words "or a specific or specific OTC drugs are";

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

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

i. In paragraph (a)(7)(ii) by removing the first and second sentences and by adding three sentences in their places;

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

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

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

- (a) * * *
- (2) * * *

OTC DRUG REVIEW INFORMATION

* * * * *

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

* * * * *

(6) * * *

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

(7) * * *

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

(ii) The Commissioner may also publish in the **Federal Register** a separate tentative order containing a statement of those active ingredients reviewed and proposed to be excluded from the monograph on the basis of the Commissioner's determination that they would result in a drug product not being generally recognized as safe and effective or would result in misbranding. This order may be published when no substantive comments in opposition to the panel report or new data and information were

received by the Food and Drug Administration under paragraph (a)(6)(iv) of this section or when the Commissioner has evaluated and concurs with a panel's recommendation that a condition be excluded from the monograph. Within 90 days, any interested person may file with the Dockets Management Branch, Food and Drug Administration, written objections specifying with particularity the provision of the tentative order to which objection is made. * * *

* * * * *

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

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

* * * * *

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

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

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

(a) *Introduction.* This section sets forth additional criteria and procedures by which 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. For purposes of this section, "condition" means an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration, marketed for a specific OTC use, except as excluded in paragraph (b)(2) of this section. For purposes of this part, "botanical drug substance" means a drug substance derived from one or more plants, algae, or macroscopic fungi, but does not include a highly purified or chemically modified substance derived from such a source.

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

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

(2) 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 Branch after deletion of information deemed confidential under 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). Sponsors must identify information that is considered confidential under these 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 Branch.

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

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

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

(2) All serious adverse drug experiences as defined in §§ 310.305 and 314.80 of this chapter, from each

country where the condition has been or is currently marketed as a prescription drug or as an OTC drug or product. Provide individual adverse drug experience reports (FDA Form 3500A or equivalent) along with a summary of all serious adverse drug experiences and expected or frequently reported side effects for the condition. Individual reports that are not in English must be translated to English in 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 generally recognized as safe and effective for OTC use in the United States, the agency will inform the sponsor and other interested parties who have submitted data of its determination by letter, a copy of which will be placed on public display in the docket established in the Dockets Management Branch. The agency will publish a notice of proposed rulemaking to include the condition in § 310.502 of this chapter.

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

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

appropriate OTC drug final monograph(s), and the condition complies with paragraph (i) of this section. 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."

Dated: January 11, 2001.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02-1457 Filed 1-22-02; 8:45 am]

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Parts 53, 301, and 602

[TD 8978]

RIN 1545-AY65

Excise Taxes on Excess Benefit Transactions

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final regulations and removal of temporary regulations.

SUMMARY: This document contains final regulations relating to the excise taxes on excess benefit transactions under section 4958 of the Internal Revenue Code, as well as certain amendments and additions to existing Income Tax Regulations affected by section 4958. Section 4958 was enacted by the

Taxpayer Bill of Rights 2. Section 4958 imposes excise taxes on any transaction that provides excess economic benefits to a person in a position to exercise substantial influence over the affairs of a public charity or a social welfare organization.

DATES: *Effective Date:* These regulations are effective January 23, 2002.

Applicability Date: These regulations apply as of January 23, 2002.

FOR FURTHER INFORMATION CONTACT: Phyllis D. Haney, (202) 622-4290 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Paperwork Reduction Act

The collections of information contained in these final regulations have been reviewed and approved by the Office of Management and Budget in accordance with the Paperwork Reduction Act (44 U.S.C. 3507) under control number 1545-1623. Responses to these collections of information are required to obtain the benefit of the rebuttable presumption that a transaction is reasonable or at fair market value.

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

The estimated annual burden per recordkeeper varies from 3 hours to 308 hours, depending on individual circumstances, with an estimated weighted average of 6 hours, 3 minutes.

Comments concerning the accuracy of this burden estimate and suggestions for reducing this burden should be sent to the Internal Revenue Service, Attn: IRS Reports Clearance Officer, W:CAR:MP:FP:S Washington, DC 20224, and to the Office of Management and Budget, Attn: Desk Officer for the Department of the Treasury, Office of Information and Regulatory Affairs, Washington, DC 20503.

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

Background

Section 4958 was added to the Internal Revenue Code (Code) by the Taxpayer Bill of Rights 2, Public Law 104-168 (110 Stat. 1452), enacted July 30, 1996. The section 4958 excise taxes generally apply to excess benefit