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Commissioner of Customs.

Approved: January 17, 2002.

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Acting Deputy Assistant Secretary of the Treasury.

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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.

FOR FURTHER INFORMATION CONTACT: John D. Lipnicki, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2222.

SUPPLEMENTARY INFORMATION: The purpose of this final rule is to establish [illegible] 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 [illegible] 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 [illegible]

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

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 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

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 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

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

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 [illegible] 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 [illegible] 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 [illegible]

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 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 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)(l)(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

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