manually. In all incidents of this type, the rudder movement can by stopped by use of the rudder pedals within the normal limits for yaw control.

Sticking conditions in the rudder trim switch if not corrected, however, could result in uncommanded movement of the rudder, and consequent deviation of the airplane from its set course.

Explanation of Relevant Service Information

The FAA has reviewed and approved Boeing Alert Service Bulletin 737–27A1198, dated June 6, 1996, which describes procedures for replacing aileron/rudder trim control module P8–43 with a new module that contains an improved switch. This improved module minimizes internal friction that has caused the sticking conditions.

Explanation of Requirements of Proposed Rule

Since an unsafe condition has been identified that is likely to exist or develop on other products of this same type design, the proposed AD would require replacing the aileron/rudder trim control module P8–43 with a new improved module. The actions would be required to be accomplished in accordance with the alert service bulletin described previously.

Cost Impact

There are approximately 1,159 Boeing Model 737–300, -400, and -500 series airplanes of the affected design in the worldwide fleet. The FAA estimates that 537 airplanes of U.S. registry would be affected by this proposed AD. Replacement of the module would take approximately 3 work hours per airplane to accomplish, at an average labor rate of $60 per work hour. Required parts would cost approximately $1,063 per airplane. Based on these figures, the cost impact of the proposed AD on U.S. operators is estimated to be $667,491, or $1,243 per airplane.

The cost impact figure discussed above is based on assumptions that no operator has yet accomplished any of the proposed requirements of this AD action, and that no operator would accomplish those actions in the future if this AD were not adopted.

Regulatory Impact

The regulations proposed herein would not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with Executive Order 12612, it is determined that this proposal would not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

For the reasons discussed above, I certify that this proposed regulation (1) is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under the DOT Regulatory Policies and Procedures (44 FR 11034, February 26, 1979); and (3) if promulgated, will not have a significant economic impact, positive or negative, on a substantial number of small entities under the criteria of the Regulatory Flexibility Act. A copy of the draft regulatory evaluation prepared for this action is contained in the Rules Docket. A copy of it may be obtained by contacting the Rules Docket at the location provided under the caption **ADDRESSES**.

List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

The Proposed Amendment

Accordingly, pursuant to the authority delegated to me by the Administrator, the Federal Aviation Administration proposes to amend part 39 of the Federal Aviation Regulations (14 CFR part 39) as follows:

PART 39—AIRWORTHINESS DIRECTIVES

1. The authority citation for part 39 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701.

§ 39.13 [Amended]

2. Section 39.13 is amended by adding the following new airworthiness directive:

Boeing: Docket 96–NM–67–AD.

Applicability: Model 737–300, -400, and -500 series airplanes; as listed in Boeing Alert Service Bulletin 737–27A1198, dated June 6, 1996; certified in any category.

Note 1: This AD applies to each airplane identified in the preceding applicability provision, regardless of whether it has been otherwise modified, altered, or repaired in the area subject to the requirements of this AD. For airplanes that have been modified, altered, or repaired so that the performance of the requirements of this AD is affected, the owner/operator must request approval for an alternative method of compliance in accordance with paragraph (b) of this AD. The request should include an assessment of the effect of the modification, alteration, or repair on the unsafe condition addressed by this AD; and, if the unsafe condition has not been eliminated, the request should include specific proposed actions to address it.

Compliance: Required as indicated, unless accomplished previously.

To prevent sticking conditions in the rudder trim switch, which could result in uncommanded movement of the rudder and consequent deviation of the airplane from its set course, accomplish the following:

(a) Within 2 years after the effective date of this AD, replace the aileron/rudder trim control module P8–43 having part number (P/N) 69–73703–5 or 69–73703–6 with a new aileron/rudder trim control module having P/N 69–73703–8, in accordance with Boeing Alert Service Bulletin 737–27A1198, dated June 6, 1996.

(b) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, Seattle Aircraft Certification Office (ACO), FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, Seattle ACO.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Seattle ACO.

(c) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Issued in Renton, Washington, on September 26, 1996.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 96–25307 Filed 10–2–96; 8:45 am]

BILLING CODE 4910–13–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 330

[Docket No. 96N–0277]

RIN 0910–AA01

Eligibility Criteria for Considering Additional Conditions in the Over-the-Counter Drug Monograph System; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is considering proposing to amend its regulations to include criteria under which certain additional over-the-counter (OTC) drug active ingredients, indications, dosage forms, dosage strengths, routes of administration, and active ingredient combinations (hereafter referred to as ''conditions'') may become eligible for inclusion in the OTC drug monograph

system. The proposed criteria would address how OTC marketing experience in the United States or abroad could be used to meet the statutory definition of marketing ''to a material extent'' and ''for a material time'' to qualify a specific OTC drug condition for consideration under the OTC drug monograph system. Under the approach being considered, once an OTC drug condition qualified for consideration in an OTC drug monograph it would be evaluated for general recognition of safety and effectiveness in accordance with the FDA regulations. The decision on whether to propose such regulations will be based, in part, on information and comments submitted in response to this advance notice of proposed rulemaking. The agency is open to approaches other than those identified in this document. FDA is specifically soliciting a broad range of comments to help it decide whether and how to propose amending its regulations to include eligibility criteria for considering additional conditions in the OTC drug monograph system.

DATES: Written comments by January 2, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–105), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2304.

SUPPLEMENTARY INFORMATION:

I. Background

A. History

1. Historical Development of the OTC Drug Monograph System

Since the passage of the Federal Food, Drug, and Cosmetic Act (the act) in 1938, submission of a new drug application (NDA) has been required before marketing a new drug. Under the 1938 act, an applicant who submitted an NDA for approval had to show that a drug product was safe for human use. The 1962 amendments to the act added the requirement that the drug be effective, as well as safe, for its intended uses.

Not all drugs are considered ''new drugs'' for which premarket approval is required. A drug is not a new drug if: (1) It is generally recognized as safe and effective under the conditions of use for which it is labeled and (2) it has been used to a material extent and for a material time under those conditions (see section 201(p) of the act (21 U.S.C. 321(p))).

To ensure that all drugs marketed in the United States met the act's requirements for efficacy imposed under the 1962 amendments, the agency undertook a review of all the drugs approved for marketing before 1962 on the basis of safety only, i.e., all products approved between 1938 and 1962. In 1966, FDA contracted with the National Academy of Sciences-National Research Council (NAS–NRC) for a review of these drugs, which were covered by ''safety'' NDA's. Thirty panels of experts examined the efficacy, by class or therapeutic category, of all drugs covered by these approved ''safety'' NDA's. The panels considered factual information from scientific literature, reports from manufacturers containing the best evidence in support of their drug efficacy claims, and information provided by FDA and other sources. The NAS–NRC panels related their conclusions to FDA, and the agency reviewed their evaluations by a procedure known as the Drug Efficacy Study Implementation (DESI) program and made efficacy determinations for the drug products.

Of the approximately 3,900 drugs that NAS–NRC reviewed, about 400 were OTC drugs. These OTC drugs were handled under the DESI program, and FDA classified some of these drugs as lacking sufficient evidence of safety and/or effectiveness and ordered their removal from the market (see § 330.12 (21 CFR 330.12)). In most cases, when deferral of implementation led to no significant risk to the public health, conclusions regarding the OTC drugs' safety and efficacy were deferred to a separate OTC drug review that FDA initiated in 1972.

In the Federal Register of May 11, 1972 (37 FR 9464), FDA established the OTC drug monograph system (currently in part 330) (21 CFR part 330). The system was established to evaluate the safety and efficacy of all OTC drug products marketed in the United States before May 11, 1972, that were not covered by NDA's, and all OTC drug products covered by ''safety'' NDA's that were marketed in the United States before the enactment of the 1962 drug amendments to the act. The OTC drug review was set up to evaluate OTC drugs by designated 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 and not misbranded.

FDA publishes these conditions in the Federal Register in the form of OTC drug monographs, which consist primarily of active ingredients, combinations of active ingredients, labeling, and other general requirements. Final monographs for OTC drugs that are generally recognized as safe and effective and not misbranded are codified in part 330. Manufacturers desiring to market a monographed condition need not seek clearance from FDA before marketing.

2. Statutory Requirements Relating to a Drug's Eligibility Under the OTC Drug Monograph System

Only drugs that are not new drugs may be covered by a monograph. As stated above, to market a new drug, an NDA must be submitted to and approved by FDA before marketing. The term ''new drug'' is defined, under section 201(p) of the act (21 U.S.C. 321(p)), 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.

The courts have interpreted section 201(p) of the act to mean that to avoid new drug preapproval requirements, the drug product must be generally recognized as safe and effective and must have been used to a material extent and for a material time under the labeled conditions of use. (See, e.g., *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631 (1973); *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F.2d 795, 801–802 (2d Cir. 1980).) To satisfy the requirements of section 201(p)(2) of the act for a particular drug, both the time and the extent of marketing of the drug must be shown to be material. In addition, as discussed in section I.A.3. of this document, the agency has interpreted the use required by section 201(p)(2) to mean use in the United States.

3. Application of the Statutory Requirements for Determining Eligibility in the OTC Drug Monograph System

As stated above, FDA considered in its review all active ingredients in OTC drug products that were on the U.S. market as of May 11, 1972, when the

review began, regardless of specific marketing history.

The agency has recognized that the ''newness'' of an OTC drug product can occur for several reasons. The newness may arise by reason, among other reasons, of the drug product's new ingredient, indication, dosage form, dosage strength, route of administration, or combination of active ingredients. (See 21 CFR 310.3(h).)

Periodically, questions would arise about whether certain conditions of use introduced after May 11, 1972, caused the products to be ''new'' drugs requiring marketing approval under NDA's, or whether the products could be eligible for consideration in the OTC drug monograph system. The agency determined the eligibility of these conditions individually on the basis of whether they had been marketed to a material extent and for a material time. Examples of the agency's past material extent and material time eligibility determinations are discussed below.

The agency has taken the position that the marketing of an OTC drug in a foreign country, but never in the United States, does not satisfy the requirement of marketing to a material extent and for a material time. In the Federal Register of December 12, 1980 (45 FR 82014), the agency concluded that menfegol, a vaginal contraceptive active ingredient marketed abroad for a number of years as an OTC drug product, was a new drug within the meaning of section 201(p) of the act because it had never been marketed as a drug in the United States. Likewise, in the Federal Register of November 16, 1988 (53 FR 46204 at 46248), the agency stated that it considered a lysine salt of aspirin, an internal analgesic active ingredient, to be a new drug within the meaning of section 201(p) of the act. This ingredient had been marketed OTC abroad but had never been marketed as a drug in the United States.

The agency also has declared new dosage strengths to be ineligible for the OTC drug review. In 1984, FDA denied a citizen petition requesting that the agency reopen the administrative record for the rulemakings for OTC internal analgesic and menstrual drug products to consider a new dosage strength of ibuprofen (200 milligrams (mg)) (Ref. 1). The agency denied the petition, stating that the 200 mg dosage strength had not been used to a material extent and for a material time in the United States and, therefore, was considered a ''new drug'' that could not be lawfully marketed in the United States without an approved NDA.

In the Federal Register of July 19, 1983 (48 FR 32872 at 32873), the agency stated that a labeled indication that had never previously appeared on any marketed OTC drug product was not eligible for consideration in the OTC drug monograph system. The agency determined that products claiming ''to minimize or prevent inebriation'' had not been marketed to a material extent and for a material time in the United States and declared that all products with sobriety aid indications were new drugs within the meaning of section 201(p) of the act.

Similarly, FDA concluded that an ingredient that had not previously been marketed in the United States for a specific indication is not eligible for consideration in the OTC drug monograph system. In the Federal Register of October 13, 1983 (48 FR 46694 at 46695), the agency stated that potassium sorbate had not been marketed to a material extent and for a material time in the United States as a vaginal drug product active ingredient and, therefore, was considered a new drug within the meaning of section 201(p) of the act for such use.

More recently the agency has found that avobenzone, a sunscreen ingredient, is eligible for review in the OTC drug monograph system (61 FR 48645, September 16, 1996). Avobenzone has been continuously marketed OTC in the United States under NDA's for approximately 8 years and subject to the NDA adverse events reporting requirements. Over 5 million units of avobenzone-containing products have been sold in the United States.

In applying the material extent and material time provision of section 201(p)(2) of the act to determine whether certain conditions were eligible for consideration in the OTC drug monograph system, FDA has also applied a ''substantially indistinguishable'' standard. This standard was first articulated in a September 23, 1977, letter to a drug manufacturer concerning its submission regarding the ingredient potassium nitrate for use as an OTC tooth desensitizing agent (Ref. 3). The letter stated that an ingredient may meet the act's marketing provision of section 201(p)(2) of the act without having been marketed under the precise conditions of use sought, provided the ingredient had been marketed to a material extent and for a material time under other conditions of use that, although different, are ''substantially indistinguishable'' in all respects relevant to the drug's safety and effectiveness. Specifically, the conditions of use would have to be similar enough that experts could reliably conclude that knowledge about the safety and effectiveness of a drug derived from experience with its use under one set of conditions could be applied to the evaluation of the safety and effectiveness of its use under the conditions for which approval was being sought.

B. Petitions and Comments

The agency has received one comment and nine citizen petitions (Refs. 4 through 13) requesting that it accept foreign marketing data to demonstrate that specific conditions of use have been marketed to a material extent and for a material time and, on that basis, to consider these conditions in the OTC drug review. If the agency were to change its current policy and accept such data, this would allow such conditions to be considered in the OTC drug monograph system.

This advance notice of proposed rulemaking addresses the primary issue raised in these petitions regarding acceptance of foreign marketing experience to demonstrate that OTC drug conditions have been marketed to a material extent and for a material time. The agency will provide separate responses to the petitions at a later date.

II. Criteria Under Consideration for Demonstrating Marketing to a Material Extent and for a Material Time

Currently, the OTC drug regulations in part 330 do not define: (1) Eligibility requirements for consideration in the monograph system or (2) what constitutes marketing to a material extent or for a material time. However, FDA's policy has been not to consider foreign marketing experience for purposes of determining whether a drug has been marketed to a material extent or for a material time. The agency is considering a proposed rule containing criteria for defining material extent and material time under which an OTC condition with or without U.S. marketing experience could be considered in the OTC drug monograph system. As previously indicated, FDA defines a condition as any active ingredient, indication, dosage form, dosage strength, route of administration, active ingredient combination, or any combination of these conditions.

In developing these criteria, FDA is considering three basic issues: (1) Nature of use, (2) time used (material time), and (3) extent of distribution (material extent).

These issues are discussed below and the agency is seeking comment on each.

A. Nature of Use

When determining if a foreign OTC drug product condition has been marketed to a material extent and for a material time, FDA is particularly concerned about certain variables presented by foreign marketing experience. In the Federal Register of February 22, 1985 (50 FR 7452), the agency amended its regulations pertaining to foreign clinical studies in § 314.106 (21 CFR 314.106) to provide specifically for the acceptance of foreign data in NDA's. In doing so, the agency acknowledged the high quality of drug testing from a number of foreign research institutions, but recognized that foreign data present three unique issues not associated with domestic data: (1) Medical, genetic, and cultural differences between countries; (2) lack of FDA's familiarity with foreign clinical investigators and facilities; and (3) FDA's inability to conduct on–site verification of many foreign studies (see 50 FR 7452 at 7483). To address these concerns, the agency specified three criteria in § 314.106 that must be met before the agency can approve an NDA based solely upon foreign data: (1) The foreign data must be applicable to the U.S. population and U.S. medical practice; (2) the studies must be performed by clinical investigators of recognized competence; and (3) the data can be considered valid without the need for on-site inspection by FDA or, if FDA considered such an inspection necessary, FDA would be able to validate the data through on-site inspection or other means. 21 CFR 312.120 contains additional acceptance criteria for foreign clinical studies not conducted under an IND.

The agency recognizes that foreign marketing experience, like foreign clinical data, presents several unique issues not associated with U.S. marketing data: (1) Medical, genetic, or cultural differences between a foreign country's population and the U.S. population may affect the way OTC drug products are used and, in turn, the medical outcomes; (2) the diversity in the way drug products are marketed in foreign countries (e.g., prescription, OTC general sales, behind the counter, sold by a pharmacist (third class of drugs)) may make it difficult to demonstrate suitability for OTC sale in the United States; and (3) many foreign countries' marketing approval processes and adverse event reporting requirements would make it difficult to determine whether adverse reactions to the OTC drug product have been experienced. Therefore, in establishing what constitutes use for a material time and to a material extent, FDA must determine whether to impose any limitations on types of marketing experience it would consider relevant to whether the drug should be marketed OTC in the United States under a monograph system. The following discussion focuses these issues on limitations related to: (1) Where the drug is marketed and its relevance to the U.S. population; (2) the type of adverse reporting system that exists in the countries in which the drug has been marketed and the nature of any adverse event reports associated with the drug; and (3) the nature of that marketing experience, such as whether the drug has been marketed by prescription, OTC, or as a third class of drugs that can be sold only by a pharmacist. This marketing experience would also be based on consistent active ingredients and product formulations that do not require critical manufacturing controls and/or involve complex bioavailability questions.

1. Where the Drug is Marketed

Because of the concerns discussed above, one petition suggested that the agency limit its consideration of OTC marketing experience to the export countries identified in section 802(b)(4)(A) of the act (21 U.S.C. 382(b)(4)(A)), as added by the Drug Export Amendments Act of 1986 (Pub. L. 99–960). Section 802(b)(4)(B) of the 1986 amendments listed four requirements related to the approval of drugs in foreign countries. These requirements were similar to requirements in the United States. Congress declared that 21 countries met these requirements and were listed in section 802(b)(4)(A) of the act for purposes of allowing them to receive for general marketing the export of certain unapproved new drugs from the United States. In April 1996, Congress amended section 802 of the act (Pub. L. 104–134) to, among other things, add additional countries to the list, allow the Secretary of Health and Human Services to add additional countries that meet certain requirements described in new section 802(b)(1)(B) of the act (formerly section 802(b)(4)(A)), and allow the export of certain unapproved drugs from the United States to any country if the drug complies with the laws of that country and has valid marketing authorization by the appropriate authority in one of the listed countries, and certain other conditions are met, as described in the new sections 802(f) and 802(g).

Although the listed countries may have similar statutory or regulatory requirements to those of the United States, other countries may also have acceptable marketing and approval processes. The agency requests specific comment on whether OTC marketing experience should be considered solely from countries listed or designated under the new section 802(b)(1) of the act or whether experience that meets certain broader criteria should be considered.

2. Adverse Event Reporting

For the agency to rely on adverse event information in assessing the safety of the condition in OTC marketing and use, the adverse event information would have to be collected in a country with a drug marketing approval process and postmarketing surveillance system that identifies serious and/or important adverse events associated with the condition's use.

To assist in making the determination regarding whether a condition has met the requirements of marketing for a material extent and for a material time, the agency is considering requiring submission of the following information: (1) A description of each country's system for identifying adverse events, especially those found in OTC marketing experience, including method of collection if applicable; (2) all serious and important adverse event reports from every country where the condition has been or is currently marketed (whether prescription or OTC); and (3) a list of all countries in which the condition has been withdrawn or in which marketing has been restricted for reasons related to safety or effectiveness, or for any other reason, and a description of these reasons.

The agency believes that prescription as well as OTC adverse event reports for the condition should be required to be included in an eligibility data submission because data on prescription adverse events may provide useful information for evaluating the safety of the condition for U.S. OTC drug use. The agency also believes that information regarding adverse events associated with other doses (higher or lower) or different indications associated with the condition marketed as a prescription drug product would be useful for determining the safety of the condition for OTC use. This information could result, for example, in different labeling or a different dosing regimen or could even suggest that the marketing of the condition under an OTC drug monograph would be inappropriate.

3. Nature of Marketing Experience

Because the criteria under consideration are to determine eligibility for consideration in the OTC monograph review, FDA must consider

whether marketing experience as a prescription drug will be considered or whether to limit the marketing experience to OTC marketing experience. FDA is considering limiting eligibility to those conditions (as defined previously) that: (1) Have been marketed for direct OTC purchase by consumers; and (2) are not limited to prescription use in the United States.

Under existing procedures in 21 CFR 310.200, conditions may attain OTC status in one of two ways:

a. As a new drug. A proposal may be initiated by the Commissioner of Food and Drugs if it is determined that agency requirements are not necessary for the protection of the public health, or by any interested person through the filing of a petition, NDA, or supplemental NDA. A drug switched to OTC status under these provisions remains a ''new drug'' unless it meets each of the necessary conditions under section 201(p)(1) and (p)(2) of the act for a drug not to be regarded as a new drug.

b. As a monograph drug. Through the OTC drug monograph system by either: (1) Recommendations made by an OTC advisory review panel or committee, (2) requests from interested parties (usually in the form of a data submission), or (3) initiated by the agency in an OTC drug monograph.

When the OTC drug review began, it was designed to address OTC marketing conditions that were already on the market in the United States. The agency permitted the OTC advisory panels to consider prescription to OTC switches and recommend OTC use for prescription drugs whose safety and efficacy for OTC use they believed had been demonstrated in the U.S. population through prior marketing experience.

Since the completion of the first phase of the OTC drug review (i.e., the OTC advisory review panels' evaluations and publication of their reports), the majority of drug manufacturers have elected to pursue switches from prescription to OTC status under the new drug procedures. The agency considers this mechanism appropriate because the data provided by an NDA, including adverse event reports, manufacturing controls, and bioavailability data where applicable, provide useful information during the transition from prescription to OTC marketing status. In addition, the mandatory reporting of adverse events under an NDA is important to the agency to monitor safe and effective OTC use once a switch has occurred.

Currently, no adverse event reporting requirements exist for drugs in the OTC drug monograph system. In a future issue of the Federal Register, the agency intends to propose to establish an adverse event reporting system for OTC monograph drugs. However, at this time, the agency believes that the transition from prescription to OTC status is best accomplished by first requiring an OTC drug product to be marketed under an NDA. After a switch occurs under an NDA and sufficient marketing experience is obtained or an adverse event reporting system is in place for OTC monograph drugs, FDA would be willing to include switched drugs in an OTC drug monograph. If and when an adverse event reporting system for OTC monograph drugs is established, this system would better support the use of OTC drug monographs for future prescription to OTC switches that do not require critical manufacturing controls for safe and effective use.

At this time, the agency does not believe that the criteria for determining material time and material extent should apply to drugs marketed by prescription in a foreign country but not marketed in the United States. Some drugs that are marketed by prescription in a foreign country were considered for approval in the United States but not approved because FDA believed that their safety and efficacy had not been proven. Furthermore, the agency believes that it is not appropriate for a drug that has characteristics that have been determined to require a prescription in a foreign country to enter directly into the OTC market in the United States when the U.S. population has no experience with the drug either on a prescription or OTC basis. The agency considers it essential that any prescription drug have some U.S. marketing experience before its OTC marketing is permitted in this country. Further, the agency believes that the criteria being considered in this document should not be applicable to establish use to a material time and to a material extent if the drug has no direct-to-consumer OTC marketing experience in any country.

OTC drugs whose marketing history shows that they were marketed in the United States without appropriate authorization would not be eligible for consideration in the OTC drug review based on the new material time and extent eligibility criteria. To treat such drugs otherwise would reward those who chose not to comply with the law.

These criteria would not apply to sustained-release products, which remain new drugs under 21 CFR 200.31 because of the difficulties associated with developing a standardized monograph that would cover the wide variety of sustained release formulations. These products almost always involve complex bioavailability/bioequivalence questions.

The agency recognizes that some of the countries listed in 802(b)(1)(A) of the act (e.g., Australia, Canada, New Zealand, and the United Kingdom) have a third class of OTC drug products that can be sold only by a pharmacist. When consumers purchase OTC drugs in this class, there is intervention by a health professional and an opportunity for professional consultation. The agency would not consider this type of OTC marketing to be similar to the broad OTC marketing in the United States, where products are marketed in many various outlets, often with no opportunity for professional consultation. The agency seeks specific comment on whether marketing in a foreign country as a third class of drugs sold by a pharmacist should be considered when evaluating whether a drug has been marketed for a material time and to a material extent.

B. Time Used (Material Time)

The agency is considering proposing that this OTC marketing be for a minimum of 5 years to satisfy the material time requirements of the act. In determining how many years should constitute marketing for a material time, the agency's principal concern is that the condition be marketed for a sufficient time to detect serious and/or important adverse events. The agency believes that a minimum 5-year timeframe should be required to provide an appropriate margin of safety to ensure that adverse event reporting is sufficient to detect almost all types of serious and/or important adverse events if sufficient volume of sales and postmarketing surveillance in this timeframe can be documented (see section II. C. of this document).

If the condition has not been marketed previously in the United States, the agency believes that the specific condition should be marketed for this 5-year minimum time period in a population demonstrated to be representative of the U.S. population (e.g., by race, gender, ethnicity, and other pertinent factors) that would be exposed to the OTC drug if it were marketed in the United States under an OTC drug monograph. Foreign marketing exposure (i.e., diversity within the user population) would have to be described sufficiently to ensure that the condition can be reasonably extrapolated to the U.S. population. Any cultural or geographic differences in the way drugs are used in the foreign country and in the United States would

be required to be explained. The agency seeks specific comment on how the representation of the population could be established.

C. Extent of Distribution (Material Extent)

The agency believes that there should be some flexibility when assessing the extent of marketing for an OTC drug product condition. Because the agency intends to consider numerous factors in determining whether the condition has been marketed to a material extent, the agency does not believe that this determination should be based solely on the sale of a certain established number of dosage units, as one petition suggested. The agency also believes that the extent of the condition's use should be sufficient to detect serious and/or important adverse events, including rare events, to demonstrate a favorable adverse event profile. The agency is considering using the following factors to evaluate whether the extent of use of a condition is sufficient to detect serious and/or important adverse events: (1) Number of dosage units sold; (2) number and types of adverse event reports, and the requirements of the reporting system; (3) risks and consequences associated with the therapeutic category and indication; (4) use pattern (frequency: Occasional, acute, chronic); (5) potential toxicity (including dosage form and route of administration); and (6) history of use (i.e., use indications and exposures, including their toxicities)

III. Implementation

A. Two-Step Application Process

The agency is considering proposing that sponsors first demonstrate that a condition meets the basic eligibility requirements of marketing to a material extent and for a material time, in the appropriate format, before the agency accepts any data in support of the condition's general recognition of safety and effectiveness. Upon evaluation of the eligibility data, the agency would notify the sponsor of its determination. If the condition were found to be eligible, the sponsor could then submit its data to demonstrate safety and effectiveness in accordance with part 330.

The agency believes that sponsors should not incur unnecessary costs for developing safety and effectiveness data for a condition of use that may not meet the basic eligibility requirements of marketing to a material extent and for a material time. In addition, the agency does not want to expend scarce resources evaluating safety and effectiveness data for a condition if it does not meet the basic eligibility criteria.

The agency notes that the advisory review panels mentioned in § 330.10(a)(1) no longer exist. Therefore, safety and effectiveness data would be reviewed on an individual basis, with the assistance of the agency's current Nonprescription Drugs Advisory Committee and other Drug Advisory Committees when deemed appropriate. If the agency determined that the data were sufficient to establish that the condition was generally recognized as safe and effective, it would then propose in the Federal Register to include the condition in an appropriate OTC drug monograph.

B. Compendial Monograph

FDA believes there is a need for publicly available chemical standards to ensure that all OTC drug products contain ingredients that are chemically equivalent to those described in an OTC monograph. To ensure that OTC drugs remain safe and effective for their intended uses, the agency believes that any ingredient included in an OTC drug monograph should also be recognized in an official compendium (e.g., the *U.S. Pharmacopeia*) setting forth its standards of identity, strength, quality, and purity. On this basis, the agency is considering proposing that no final monograph be issued and no interim marketing be allowed until there is an official compendial monograph that is consistent with the marketed ingredients used to establish general recognition of safety and effectiveness.

C. Marketing Policy

All new drugs and drugs marketed under an OTC monograph must be demonstrated to be safe and effective before they may be marketed in the United States. Although conditions evaluated under the OTC drug review were permitted to remain on the market during the review process in view of their long history of use in this country, the agency believes that allowing the marketing of a new condition before the agency has evaluated its safety and effectiveness would subject the public to unnecessary risk. Therefore, the agency is considering permitting a new condition to be marketed only after the Commissioner tentatively determines that the condition is generally recognized as safe and effective and publishes this conclusion in the Federal Register as a proposal for comment. Marketing could only occur after the comments are reviewed and an appropriate notice allowing such marketing is published in the Federal Register or after inclusion of the condition in the appropriate OTC drug final monograph.

Any interim marketing that might be allowed, pending issuance of a final rule, would be subject to the risk that the Commissioner could adopt a different position in the final rule that would require relabeling, recall, or other regulatory action. The agency seeks specific comment on this marketing policy.

IV. Analysis of Impacts

The agency also seeks specific comment regarding any substantial or significant economic benefit or impact that this rulemaking would have on manufacturers or consumers of OTC drug products. Comments regarding the benefit or impact of this rulemaking on such manufacturers or consumers should be accompanied by appropriate documentation. The agency will evaluate any comments and supporting data that are received and will assess the economic impact of this rulemaking in the preamble to the proposed rule.

V. Requests for Comments

Interested persons may, on or before January 2, 1997 submit to the Dockets Management Branch (address above) written comments regarding this advance notice of proposed rulemaking. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VI. References

The following references have been placed 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. PDN2, Docket No. 77N–0094, Dockets Management Branch.

(2) Letter from Thomas Scarlett, Associate Chief Counsel for Enforcement, Bureau of Drugs, FDA, to Harris O. Cutler, Richardson-Merrell, Inc., September 23, 1977.

(3) Comment No. CP1, Docket No. 78N–0038, Dockets Management Branch.

(4) Comment No. CP2, Docket No. 78N–0038, Dockets Management Branch.

(5) Comment No. CP3, Docket No. 78N–0038, Dockets Management Branch.

(6) Comment No. CP4, Docket No. 78N–0038, Dockets Management Branch.

(7) Comment No. C105, Docket No. 78N–0038, Dockets Management Branch.

(8) Comment No. CP1, Docket No. 81N–0033, Dockets Management Branch.

(9) Comment No. CP1, Docket No. 92P–0309, Dockets Management Branch.
(10) Comment No. CP1, Docket No. 94P–0215, Dockets Management Branch.
(11) Comment No. CP2, Docket No. 94P–0215, Dockets Management Branch.
(12) Comment No. CP1, Docket No. 95P–0145, Dockets Management Branch.

This advanced notice of proposed rulemaking is issued under sections 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371) and under the authority of the Commissioner of Food and Drugs.

Dated: September 26, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–25259 Filed 10–2–96; 8:45 am]

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DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Part 913

[SPATS No. IL–095–FOR]

Illinois Regulatory Program

AGENCY: Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

ACTION: Proposed rule; withdrawal of proposed amendment.

SUMMARY: OSM is announcing the withdrawal of a proposed amendment to the Illinois regulatory program (hereinafter the ''Illinois program'') under the Surface Mining Control and Reclamation Act of 1977 (SMCRA). The proposed amendment concerned addition of a definition for the term ''Generally accepted accounting principles'' to title 62 of the Illinois Administrative Code (IAC) regulations pertaining to self-bonding. Illinois is withdrawing the amendment at its own initiative.

FOR FURTHER INFORMATION CONTACT: Roger W. Calhoun, Director, Indianapolis Field Office, Telephone: (317) 226–6700.

SUPPLEMENTARY INFORMATION: By letter dated July 16, 1996 (Administrative Record No. IL–1804), Illinois submitted a proposed amendment to its program pursuant to SMCRA. The amendment concerned addition of a definition for the term ''Generally accepted accounting principles'' at 62 IAC 1800.23(a). Illinois submitted the proposed amendment at its own initiative.

On July 30, 1996, OSM announced receipt of and solicited public comment on the proposed amendment in the Federal Register (61 FR 39612). The public comment period ended on August 29, 1996.

On September 20, 1996 (Administrative Record No. IL–1811), Illinois requested that the proposed amendment be withdrawn. Illinois has decided not to add this definition to its regulations at this time. Therefore, the proposed amendment announced in the July 30, 1996, Federal Register is withdrawn.

List of Subjects in 30 CFR Part 913

Intergovernmental relations, Surface mining, Underground mining.

Dated: September 25, 1996.

Brent Wahlquist,

Regional Director, Mid-Continent Regional Coordinating Center.

[FR Doc. 96–25340 Filed 10–2–96; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[CO–001–002; CO–001–003 and CO–001–004; FRL–5628–8]

Clean Air Act Approval and Promulgation of PM_{10} Implementation Plan for Denver, CO, and the Denver Mobile Source Emissions Budgets for PM_{10} and NO_X

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of proposed rulemaking.

SUMMARY: EPA proposes approval of the state implementation plan (SIP) revision submitted by Colorado on March 30, 1995, to achieve attainment of the National Ambient Air Quality Standards (NAAQS) for particulate matter with an aerodynamic diameter less than or equal to a nominal 10 micrometers (PM_{10}) in the Denver area, including: Control measures; technical analysis (*e.g.*, emission inventory, and attainment) and other Clean Air Act (Act) SIP requirements. The SIP revision was submitted to satisfy certain Federal requirements for an approvable moderate nonattainment area PM_{10} SIP for Denver and, among other things, contains enforceable control measures.

EPA also proposes to approve the PM_{10} and NO_X mobile source emissions budgets for Denver that were submitted by the Governor on July 18, 1995 and April 22, 1996, respectively.

DATES: Comments on the actions proposed in this document must be received in writing by December 2, 1996.

ADDRESSES: Comments should be addressed to: Richard R. Long, Director, Air Program (8P2–A), Environmental Protection Agency, Region VIII, 999 18th Street, Suite 500, Denver, Colorado 80202–2466. Label the comments as comments addressing the Denver PM_{10}, PM_{10} emissions budget or NO_X emissions budget SIPs.

Copies of the State's submittals and other information are available for inspection during normal business hours at the following locations: Environmental Protection Agency, Region VIII, Air Program, 999 18th Street, Denver, Colorado 80202–2466; and Colorado Air Pollution Control Division, 4300 Cherry Creek Dr. South, Denver, Colorado 80222–1530.

FOR FURTHER INFORMATION CONTACT: Callie Videtich, Air Program, EPA Region VIII, 999 18th Street, Suite 500, Denver, Colorado 80220–2405 or by phone at (303) 312–6434.

SUPPLEMENTARY INFORMATION:

I. Background

The Denver, Colorado area was designated nonattainment for PM_{10} and classified as moderate under sections 107(d)(4)(B) and 188(a) of the Act, upon enactment of the Clean Air Act Amendments of 1990.[1] See 56 FR 56694 (Nov. 6, 1991); and 40 CFR 81.306 (specifying PM_{10} nonattainment designation for the Denver metropolitan area). The air quality planning requirements for moderate PM_{10} nonattainment areas are set out in Part D, Subparts 1 and 4, of Title I of the Act.[2]

The EPA has issued a ''General Preamble'' describing EPA's preliminary views on how EPA intends to review SIPs and SIP revisions submitted under Title I of the Act, including those State submittals containing moderate PM_{10} nonattainment area SIP requirements (see generally 57 FR 13498 (April 16, 1992) and 57 FR 18070 (April 28, 1992)). Because EPA is describing its interpretations here only in broad terms, the reader should refer to the General Preamble for a more detailed discussion

[1] The 1990 Amendments to the Clean Air Act made significant changes to the Act. See Pub. L. 101–549, 104 Stat. 2399. References herein are to the Clean Air Act, as amended (''the Act''). The Clean Air Act is codified, as amended, in the U.S. Code at 42 U.S.C. 7401, *et seq.*

[2] Subpart 1 contains provisions applicable to nonattainment areas generally and Subpart 4 contains provisions specifically applicable to PM_{10} nonattainment areas. At times, Subpart 1 and Subpart 4 overlap or conflict. EPA has attempted to clarify the relationship among these provisions in the ''General Preamble'' and, as appropriate, in today's notice and supporting information.