DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 330

[Docket No. 80N-0094]

Over-the-Counter (OTC) Human Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded; Revision of Procedures Relating to Category III

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising the procedural regulations for reviewing and classifying over-the-counter (OTC) drugs to delete the provision that authorizes the marketing of a Category III ingredient or other condition in an OTC drug product after a final monograph. (Category III drugs are those for which there are insufficient data to establish general recognition of safety and effectiveness.) This revision affects the time period during which new data may be submitted to FDA to support the inclusion in a final monograph of a condition not classified in Category I in a proposed monograph or tentative final monograph. The agency is taking this action to conform to the court order issued by the United States District Court for the District of Columbia.

EFFECTIVE DATE: November 30, 1981.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 13, 1980 (45 FR 31422), FDA proposed to revise the OTC procedural regulations (21 CFR 330.10) to delete the provision that authorizes the marketing of a Category III ingredient or other condition in an OTC drug product after a final monograph is established. This action was taken to conform to the holding and order of the United States District Court for the District of Columbia in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). This revision affects the time period during which new data may be submitted to FDA to support the inclusion in a final monograph of those ingredients or indications for use not classified in Category I in a proposed or tentative final monograph.

The agency also announced in the May 13, 1980, proposed rule, a general enforcement policy for initiating regulatory action against those marketed OTC drug products failing to meet monograph conditions.

FDA allowed interested persons 60 days to comment on the proposal. The agency received letters from 14 different sources, including manufacturers, trade associations, consumer organizations, an individual, and a university. The substantive comments received and the agency's conclusions about them are discussed below.

General

1. One comment objected to the proposed revised regulation because it would not significantly expedite the OTC drug review. The comment argued that under the current OTC drug regulations there is no justification for allowing so many opportunities for comment and requiring so many levels of review. The comment suggested amending the regulations to allow one 60-day comment period following publication of the proposed order, which would be followed by a final monograph. The comment argued that this approach would incorporate the opportunity for public comment which FDA typically allows during rulemaking proceedings and that it would expedite the OTC drug review by eliminating the need to prepare a third **Federal Register** document for each group of drugs, and by eliminating a round of comments which now FDA must review. The comment also suggested that, under this approach, FDA allow interested persons 60 days from the effective date of the revised Category III final order to comment on any panel reports or tentative final monographs which were published before adopting the revised rule. An additional opportunity for comment would be justified only when the agency disagrees with the panel and finds an ingredient or labeling claim not generally recognized as safe and effective.

The approach suggested by the comment has been proposed a number of times and has been discussed extensively by the agency. Although FDA agrees that the OTC review could have been structured to omit the tentative final monograph, as the comment recommends, that approach was rejected when the agency established the Review for two reasons. First, the agency recognized that the OTC drug review process vitally affects the interests of OTC drug manufacturers and the public and that procedural fairness is essential to guaranteeing substantive fairness. FDA's procedures for reviewing OTC drugs were cited by the Supreme Court in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973) when the Court held that the agency had the authority to decide with administrative finality the new drug status of drug products. The procedures provided in the OTC drug review regulations, including this revision, are designed to assure that all interested persons have an opportunity to express their views at each stage of the process and to have their comments and objections reviewed by the agency before the publication of a final monograph. Second, the Panel reports, when published, have not been evaluated by FDA, but rather are the recommendations of an independent advisory committee composed of outside experts. Under the rules for the OTC review (21 CFR 330.10(a)(6)), the Commissioner of Food and Drugs may publish a proposed order containing the panel's recommendation for comment "before undertaking his own evaluation and decision on the matters involved." FDA has followed this procedure in almost all cases up to now in publishing panel reports. Thus, the proposed order containing the Panel report does not constitute FDA's proposed rule, but is an advance notice of proposed rulemaking; FDA's evaluation and position as an agency is stated for the first time in the tentative final monograph (TFM).

For FDA to implement the approach advocated by the comment, FDA would have to review and evaluate the Panel report in detail before publication and to decide whether to accept or reject every recommendation in turn. This process would consume considerable time.

Moreover, all but one of the Panels have completed their work and most of their reports have been published in the **Federal Register.** Since these reports were in most cases published without the agency's having evaluated the Panel's recommendations, it would be inappropriate for the agency simply to issue a final rule based on comments on the Panel's recommendations. The agency's proposal may differ from the Panel's recommendations as a result of the comments received and the agency's review. Even if no changes are made, the public should have notice of the agency's position on the matter and have an opportunity to respond to it before a final rule is adopted. The public receives that opportunity through the publication of the TFM. If this opportunity were not provided through publication of the TFM, an alternative opportunity would be needed to give the public notice of the agency's position before a final rule is adopted. It is FDA's view that any alternative opportunity, such as an agency review and proposed affirmation or rejection of published

Panel recommendations, would consume as much time as publishing the TFM. In sum, such an approach would be just as time consuming as that adopted in this regulation.

FDA disagrees with the comment that this new procedure will not result in significantly speeding up the Review. Under the original procedural regulations, the formal administrative process for an OTC drug product with a Category III condition extended beyond the final monograph because manufacturers were permitted to continue marketing of such a product pending development of data to support approval of the ingredient or indication for use as generally recognized as safe and effective and not misbranded. Under the revised procedure, the formal administrative process ends with the establishment of a final monograph. Thus, the agency believes that these revised procedures will expedite the OTC drug review process and still provide all interested persons with a fair opportunity for comment.

2. One comment urged that panels take a more reasonable approach to evaluating efficacy data so that ingredients long established as effective will not be relegated to Category III because they lack the kinds of studies that would be required by FDA for a new drug, without marketing experience, that was the subject of a new drug application (NDA) submitted for approval under the new drug approval process. The comment said that it is unreasonable for the panels to ignore the substantial evidence of effectiveness of ingredients derived from long-term use in the marketplace.

The agency advises that the effectiveness standards described in 21 CFR 330.10(a)(4)(ii) were adopted because they represent what medical scientists today consider to be adequate proof of effectiveness. Each panel will initially determine what level of proof is necessary, based on its expertise and experience, to demonstrate effectiveness for a particular drug. FDA will require adequate and well-controlled studies except where the agency waives this requirement as unnecessary or inappropriate. The agency advises that § 330.10(a)(4)(ii) does permit reports of significant human experience during marketing to be used as corroborative support for general recognition of effectiveness.

3. One comment suggested that the regulation be amended to permit submission of data that would allow finished OTC drug products and/or ingredients to be upgraded to Category I. According to the comment, action of this type at this point in the OTC drug review procedure would minimize the number of comments as each monograph is published. The comment argued that safety and efficacy questions should be resolved in terms of the finished OTC product, not in terms of individual ingredients which may be present in the OTC product in very low concentrations where they would not necessarily present a hazard to the user at the use concentrations. Further, the comment said that it is difficult for a manufacturer of a basic chemical that is put into Category II or III to determine the safety and efficacy of that individual chemical in a finished OTC drug product without knowledge of the product in question. The comment also objected to the OTC drug review practice of coding submissions without reference to product name or manufacturer, which in the comment's view makes it virtually impossible for a chemical manufacturer to either furnish data or to determine what data are necessary to change an ingredient from Category III to Category I.

At the beginning of the OTC drug review, the agency determined that the therapeutic category ingredient review approach was fairer and more efficient than a product-by-product approach. The agency's justification for this approach was discussed thoroughly in the proposal establishing the OTC drug review process (37 FR 85; January 5, 1972) and in response to comments in the final rule (37 FR 9464; May 11, 1972). The safety and effectiveness of an ingredient are each determined on the basis of that ingredient's intended use. Information submitted to panels for their consideration may include data on the safety and effectiveness of individual active ingredients as well as data on the safety and effectiveness of finished drug products. Published panel reports list all firms that submitted data to the panels and any marketed products to which the data relate. In addition, a panel's administrative file, which has an index of all submissions, including firms and marketed products, is placed on public display in the FDA Dockets Management Branch (formerly the Hearing Clerk's office) 30 days after a panel report is published. Thus, any interested person would have access to that information.

Testing of Category III Conditions

4. Two comments, in noting that the agency will no longer include recommended testing guidelines in tentative final and final monographs, expressed concern that testing guidelines developed by panels will be discarded. The comments urged that panels still in existence be encouraged, as in the past, to develop testing guidelines, and if guidelines presently exist (that is, are either developed by panels or by FDA), they should be published with a panel's report for others to use if they choose in devising test protocols.

One comment argued that there is no explanation in FDA's preamble as to why these guidelines will no longer be part of tentative final and final monographs. The comment stated that the agency's failure to "articulate reasons for departure" from its earlier practice constitutes improper administrative action. The comment cited the decision in *Rhodia, Inc.* v. *FDA*, 608 F.2d 1376 (D.C. Cir. 1979) in support of this argument. According to the comment, both equitable and legal considerations mandate including testing guidelines in OTC drug monographs. The comment further contended that if a panel's proposed testing guidelines are not retained, FDA should issue a notice, either in the preamble to the proposed monograph or in a separate Federal Register document, setting forth the reasons for such action, and providing industry with an opportunity to comment. The comment pointed out that the industry's single greatest expenditure of time with the panels has been in the development of appropriate testing guidelines, and that it is unfair for FDA to exclude from the monographs this important work. Further, the comment said, it was unfair and improper for FDA to begin to publish tentative final monographs without including testing guidelines for Category III conditions until FDA first publishes proposed regulations detailing its informal procedures for consulting with industry on testing guidelines and provides opportunity for public comment.

FDA advises that neither the Federal Food, Drug, and Cosmetic Act (the act) nor the OTC regulations promulgated thereunder require testing guidelines to be published as part of OTC panel reports or tentative final monographs. In the past, panels have recommended and may continue to recommend in their reports the type of further testing required to upgrade Category III ingredients or other conditions and the time period within which such testing might reasonably be concluded. If panels do recommend testing guidelines, these guidelines will continue to be published as part of the panel report.

Panels have and may continue to recommend guidelines for the testing of those drugs that do not already have adequate tests in order to be generally recognized as effective. Previously,

under the agency's rules, that additional testing could be done after a final rule was issued finding the product to be Category III. As the court determined in *Cutler*, it is not legally permissible for the agency to authorize those products to remain on the market while additional testing is conducted when the products have been determined under a final rule not to be in compliance with the act.

The principal purpose of the OTC review is to determine which OTC drug products comply with the law and which do not. It is the responsibility of the manufacturer of a drug to have adequate tests that meet the statutory requirements before marketing the drug. Providing testing guidelines in the preamble to the TFM requires additional resources and time, and could lead to delay in the issuance of the TFM. The agency intends to focus its efforts in drafting the TFM on making an appropriate determination of whether products presently comply with the law, rather than on providing advice as an agency on the type of additional testing that needs to be done on noncomplying products to bring them into compliance.

Furthermore, FDA believes that there may be Category III conditions that industry is not interested in upgrading to Category I status. Therefore, it would be a waste of the agency's resources to review guidelines that will not be used. Testing guidelines have been included in panel reports and in the agency's preamble to the TFM only as suggestions for industry. The guidelines have never been a part of an OTC rule, nor were the guidelines binding on industry. FDA does recognize, however, the value of some kind of communication between industry and FDA Bureau of Drugs' scientists, to the extent agency resources permit, on the tests industry plans to do.

Accordingly, FDA is publishing elsewhere in this issue of the **Federal Register** a notice describing the manner in which the agency intends to communicate with industry in response to industry requests on testing guidelines, protocols, and test data. The preamble to the May 13, 1980, proposed rule stated the purpose and major feature of the agency policy in making these communications, and the notice provides further details. The notice also offers interested persons the opportunity to comment on the notice for 60 days. Comments received will be considered in any agency decision to amend or modify the policy. Any comments on the notice will be reviewed promptly, and any changes that are warranted will be made.

The agency emphasizes that FDA intends to meet with manufacturers at their request and as early in the OTC drug review process as possible to discuss protocols and other testing issues involving those conditions that industry is interested in upgrading. As before, FDA encourages manufacturers to work with one another to arrange for the necessary studies, and thus avoid unnecessary human testing.

5. One comment expressed concern that publication of tentative final monographs without testing guidelines would have the effect of delaying the start of any needed testing. Under FDA's new policy statement (published elsewhere in this issue of the **Federal Register**), prior to beginning testing the manufacturer may initiate informal communications with FDA to develop testing guidelines. The comment argues that this procedure may consume considerable time. Furthermore, the comment said FDA has drastically foreshortened the endpoint allowed for completion of testing by allowing only 1 year after publication of a tentative final monograph for the submission of new data. A manufacturer may not be told by FDA until the tentative final monograph issues that it must do further testing, and at that stage a manufacturer would be allowed only 1 year to submit results, even though the testing may reasonably require far more than 1 year to complete. The comment suggested the following alternatives to FDA's proposal:

a. In appropriate cases, instead of closing the record for submission of new data 1 year after publishing a tentative final monograph, FDA should leave the record open as needed for completion of certain specific studies that have been promised for completion, and delay issuing a final monograph during this period. The comment stated that there is no requirement in *Cutler* v. *Kennedy* that the agency publish a final monograph until all pertinent ongoing studies have been completed and considered by the agency.

b. A final monograph need not address all conditions encompassed by the affected class of drugs, but rather only those conditions for which FDA has reached final conclusions. Other conditions of use, for which further administrative consideration properly is pending, need not be addressed in a final monograph until their administrative consideration is completed. Such action would not violate *Cutler* v. *Kennedy* because rulemaking would be pending on those conditions for which further data were needed, and no final monograph would be issued ruling on such conditions (or establishing any inference with respect to their legality) until the agency reviewed the relevant data. The comment pointed out that FDA's proposal already sets a precedent for separately addressing distinct conditions of use in successive monographs by proceeding with separate orders for certain Category II conditions within a class of drug product, without waiting to rule on the other conditions of use.

As explained in the response to comment 4 above, testing guidelines will continue to be published as part of panel reports if panels have recommended such guidelines. Further, as stated above, the agency intends to meet with manufacturers at their request and as early in the OTC review process as possible to discuss protocols and other testing issues involving those conditions that industry is interested in upgrading. Thus, FDA does not agree that publishing tentative final monographs without testing guidelines, where such guidelines have been recommended by a panel, will delay any necessary testing.

The agency is committed to completing the OTC drug review expeditiously. The regulations under § 330.10 establish an orderly administrative process for accomplishing this review. Once FDA has established its final position on a category of OTC drug products by publishing a final monograph, any OTC drug product not in compliance with an applicable monograph or not covered by an approved new drug application is subject to regulatory action. FDA does not intend to delay the OTC drug review administrative process while manufacturers complete studies and submit the test data to the agency for review and evaluation. Thus, the alternative approaches proposed by the comment are not acceptable. The agency recognizes that industry believes strongly that there may be extraordinary circumstances which may warrant FDA's consideration of reopening of an administrative record. Under revised § 330.10(a)(7)(v), the agency may consider data submitted after the administrative record has closed and before the final monograph is published if the Commissioner finds good cause has been shown. The agency will consider requests for the reopening of an administrative record on a case-by-case basis.

Contents and Time of Closing of the Administrative Record

6. One comment argued that the proposed 12-month testing period is just as inconsistent with the act as the

Category III regulation which Judge Sirica held to be illegal. The comment stated that in both situations, the act requires that OTC drugs first sold after 1962 be generally recognized as safe and effective before they are placed on the market. The comment stated that the Supreme Court held in *Weinberger* v. *Hynson, Westcott and Dunning,* 412 U.S. 609 (1973) that the manufacturer of any drug marketed pursuant to the generally recognized as safe and effective exception (and this includes virtually all OTC drugs) must be able to show by "substantial evidence" that the drug is "safe and effective," and, in addition, that there is an "expert consensus" that the drug is safe and effective. 412 U.S. at 629–632. The comment further stated that the Court reaffirmed this standard recently in *United States* v. *Rutherford,* 441 U.S. 544, 549–550 n. 7 (1979). The comment argued that Judge Sirica found that the Category III regulation was illegal because it authorized the marketing of OTC drugs even though FDA had found that those drugs lacked evidence adequate to find them generally recognized as safe and effective. Because they were not generally recognized as safe and effective, as required by the act, FDA could not authorize their sale. This revised rule would specifically delay any administrative action, including the final monograph, pending a 1-year testing period which follows the agency's tentative conclusion (expressed in the tentative final monograph) that the drug is not generally recognized as safe and effective. In the face of that tentative conclusion, it cannot be said that there is an "expert consensus" that the drug is "safe and effective." Therefore, sale of the drug is illegal under *Hynson,* and FDA has no authority to adopt regulations that would delay final action on such drugs pending testing.

The comment is correct that the act requires that OTC drugs sold after 1962 be generally recognized as safe and effective. Indeed, the OTC Drug Review was set up to determine in as fair and efficient a manner as possible which OTC drugs can be so recognized.

The comment's reliance on *Cutler* in support of its position, however, is inapposite. Judge Sirica did not address the legal status of OTC products containing a Category III condition during the rulemaking process; the court addressed only the status after publication of a final order. Moreover, FDA does not "authorize" the marketing of OTC drugs during the pendency of the rulemaking. The final monograph for each therapeutic class will constitute the agency's position on the generally recognized as safe/generally recognized as effective (GRAS/GRAE) status of products containing ingredients within its scope. Until a final monograph has issued, however, the legal status of products containing ingredients within its scope is the same as it was before the Review began. They are either GRAS/GRAE or they are not.

The comment incorrectly assumes that the 12-month period following the tentative final monograph is for the sole purpose of giving manufacturers additional time for testing to upgrade a condition to Category I status. Rather, that period is the fixed time during which persons may submit data to the agency without petitioning to reopen the administrative record. These data may consist of additional data and information that FDA, either from informal meetings with manufacturers to discuss testing requirements or after a review of previously submitted data, has determined are necessary to upgrade a condition to Category I. In addition, manufacturers may submit new data from testing previously conducted. Finally, FDA rejects the argument that these revisions to the OTC procedural regulations will delay the final administrative decision on a particular class of ingredients. As stated in the preamble to the May 13, 1980, proposed rule, based on the agency's experience with comments filed to panel reports and with objections and requests for a hearing filed in response to the tentative final and final monographs published to date, the time necessary for the agency to conduct essential scientific and administrative review and evaluations that must be completed before a final rule is issued is at least 12 months. The agency expends a substantial amount of time on the administrative review and evaluation of the grounds for objections and responding to these objections, on reviewing and responding to requests for hearings, and on the preparation and conduct of any hearings that are warranted. The agency also reviews and evaluates new data as they are received. These scientific and administrative reviews and evaluations by the agency proceed on parallel, not sequential, tracks with the time permitted for the submission of new data. Therefore, permitting the administrative record to remain open for a fixed time period following a tentative final monograph will not, in the agency's judgment, delay the overall OTC drug review process.

7. One comment argued that the presumptions in the justifications for this new regulatory scheme, that "manufacturers must, in the future, submit, before the final monograph, the data necessary to resolve the issues that previously resulted in a Category III classification" and that "were the administrative record to remain closed, each particle of new information would have to be submitted with a petition to reopen the administrative record," are not required by law. They are based on FDA's own procedures, including the procedures proposed to be established by the proposed rule. The comment suggested that the agency could and should have proposed that the monograph become final shortly after the comment period on the tentative final monograph, providing only enough time for FDA evaluation of the comments. Any new data relating to safety and effectiveness could be treated separately. The comment further suggested that FDA could and should have proposed a procedure that permits "each new particle of information" submitted to establish safety and efficacy to be submitted for evaluation without a petition to reopen the formal record. This procedure should leave the decision with the manufacturer to determine when it believes enough such particles of information have been submitted that are not questioned by FDA to justify a petition to reopen and amend the administrative record. Use of this procedure would eliminate the unnecessarily burdensome administrative workload that the proposed rule assumes would otherwise result.

The agency's justification for the procedures provided in the OTC drug review regulations, including this revision, is addressed in the responses to comments 1 and 6 above. For the reasons set forth in those responses, FDA rejects the suggestion that FDA is providing more time than is necessary after a tentative final monograph for its evaluation of comments before publishing a final monograph.

Concerning the comment on reopening of the administrative record, FDA advises that it is standard procedural practice before all administrative bodies and courts that the record in any proceeding be closed at some specified time in order to prevent continuous submission of new data and information. Thereafter in the proceeding, arguments and decisions may be made solely on the basis of the data and information already contained in the record. Court appeal will be based solely on that record and the information it contains. The time specified for closing of the administrative record after a proposed monograph and after a tentative final

monograph is consistent with standard procedural practice. Permission to submit additional data or information may be granted, at the discretion of the Commissioner, on the basis of a petition to reopen the administrative record to include such material.

8. Comments on proposed § 330.10(a)(7)(iii) urged the agency to provide for the granting of extensions beyond the 12-month period after a tentative final monograph for the submission of new data and information. The comment argued that in some instances 12 months may be insufficient for Category III testing, for example: (1) when it is necessary to develop methodology for testing which does not now exist, panels have generally recommended not less than 2 years and up to 4 or 5 years for Category III testing in these cases; (2) the time period necessary for the development of protocols for the testing of seasonal products such as cough and cold products and sunscreen agents may be lengthened considerably by their seasonality, because test protocols are frequently designed by running preliminary tests using different protocols and designing the final protocol from the knowledge obtained from running the earlier tests; (3) animal testing to resolve Category III safety issues may have to await the development of methodology and may involve long-term studies which take more than a year; and (4) testing time may be lengthened by difficulties in recruiting investigators or testing facilities. Another comment said it would be virtually impossible to complete, let alone prepare a written presentation of, studies during that 12-month interval.

One comment argued that a small company cannot afford the immense costs involved in developing experimental methodology and validating such methodology clinically. A time period of, for example, 5 years which was permitted for Category III testing in cough/cold products, would enable a small company to draw on the experience and expertise of larger companies in developing suitable protocols and methodology and permit the small company to focus its entire attention and limited resources in undertaking the necessary clinical studies while having the benefit of much needed time over which to spread those new investigative costs and make them more affordable.

A comment argued that a period of 24 months following a tentative final monograph is the minimum time that is reasonable for interested persons to evaluate the comments stating the basis for Category III classification, devise a test program and protocols, consult with FDA as to whether the proposed test program and protocols meet FDA criteria for well-controlled studies that will meet the standards to satisfy a Category I classification, implement and carry out studies, process and evaluate resulting data, and submit data in proper form to FDA. Further, the comment argued that no significant risk to the public health will result from the additional 12-month period because a Category III ingredient usually has been marketed and used for many years, with substantial documentation of safety and requires only substantiating probable efficacy, with well-controlled studies or data.

The agency advises that under the provisions of 21 CFR 10.30 and 330.10(a)(10) any interested person may petition to reopen the administrative record to include new data at any time during the OTC drug review administrative process. The provisions of § 330.10(a)(7)(v) have been revised to clarify that the Commissioner may consider new data after the ordinary time for submissions if good cause to do so has been shown, for example, when a TFM proposes to reclassify an ingredient as Category III even though the Panel considered it Category I. The Commissioner will allow reopening of the record only in extraordinary cases. Thus most records will remain closed. The petition must demonstrate good cause why the new data could not be obtained and submitted within the time specified by § 330.10(a)(7)(iii) of this final rule. The Commissioner may grant or deny the petition at the Commissioner's discretion.

The agency is not persuaded by the reasons given by the comments for revising the regulation to provide for general extensions of the 12-month period. Manufacturers have, in most cases, been aware of Category III classification since the publication of panel reports. Substantial numbers of tests aimed at upgrading Category III conditions to Category I have already been completed and the results submitted to FDA for review and evaluation prior to publication of the relevant tentative final or final monograph. Under the agency's policy described in the notice published elsewhere in this issue of the **Federal Register**, the FDA Bureau of Drugs will inform manufacturers of its tentative determination that additional data are needed or that the data submitted are adequate to establish Category I status so that further testing appears unnecessary. Further, the agency has consistently emphasized that each manufacturer of a product with a Category III condition need not undertake the necessary testing. The agency has always encouraged firms to cooperate, in an open and nonrestrictive manner, and to work with each other or with trade associations in arranging for the necessary studies.

Regarding the concern that methodology may not always exist, FDA advises that some classes of drug products in the OTC drug review are also classes of drug products that have been approved under the new drug approval process, for example, cough/cold products or other seasonal products. Methodology used for testing safety and effectiveness for the approval of new drugs can also be used for testing OTC drug products containing ingredients in the OTC drug review.

9. One comment asserted that the 12-month period for reopening the administrative record after the tentative final monograph may not afford sufficient time to gather and to submit new data and suggested that this could be resolved by making drafts of monographs available for inspection but not comment.

The agency advises that the "information copy" of each panel's draft report, containing all the Panel's recommendations on a particular therapeutic class is routinely made available in the Dockets Management Branch, prior to the panel's acceptance of its report at the final panel meeting. The agency concludes, however, that tenative final and final monographs should not be made publicly available until the agency has reviewed and evaluated all relevant material and published its decision in the **Federal Register**. Drafts of any document still being reviewed within the agency do not represent an agency decision, and therefore it would not be appropriate to make such a document publicly available.

10. One comment suggested that because the tenative final order provides the initial notice of FDA's views, as distinguished from the views of the advisory review panel, it would be appropriate to invite comments, not just objections, concerning all aspects of a tentative final monograph, including general discussions with respect to policy, etc. Furthermore, the comment suggested that FDA provide 90 days instead of 60 days for comment in response to a tentative final monograph, the same time period provided for comment in response to a "proposed monograph." An extension of the

comment period from 60 to 90 days would not delay FDA action because the agency already proposes to keep the record open for the submission of additional scientific data, and comments upon such data, for 14 months after publication of the tentative final monograph.

The agency has amended the regulation (§ 330.10(a)(7)(i)) to allow comments as well as objections and requests for hearings to be filed within the 60-day period following publication of a tentative final monograph. The agency notes that comments on the published panel report and proposed monograph are invited in order to provide an opportunity for full public comment before the agency reaches its tentative decision on the matters involved. The agency continues to encourage all interested persons to comment fully on the proposed monograph and not to delay offering suggestions until the agency's tentative final monograph has been published. The agency rejects the suggestion to provide for a 90-day comment period. FDA believes that, especially in view of the prior opportunities for discussion and comment on the issues before and after publication of the panel report and proposed monograph, the 60-day period now provided is adequate for both the filing of objections and comments to a tentative final monograph.

11. Two comments urged that because FDA acknowledges the importance of maintaining an open administrative record, the administrative records of the five published tentative final monographs be reopened upon publication of this final rule to allow 12 months for the submission of new data and information and 2 months for comments on that data. The comments contended that, without such a reopening of the record, manufacturers of products now subject to those tentative final monographs may have little or no time to meet with FDA to develop testing guidelines or review protocols between the effective date of this final rule and the closing of the 12-month or 2-month period applicable to a given tentative final order. Another comment urged that FDA allow no more than 2 additional months for comment on any tentative final monograph which has been published between FDA's notice of intent (44 FR 61608; October 26, 1979) and publication of this final rule.

The agency rejects the comment to reopen the administrative record for previously published tentative final monographs at this time. FDA believes that manufacturers have already had ample opportunity to conduct the necessary studies for those ingredients or other conditions which they are interested in upgrading and to submit the data to the agency for review. As discussed in the response to comment 8 above, manufacturers have, in most cases, been aware of Category II and III classifications since publication of the respective panel reports. Further, the administrative records for Topical Antimicrobial, Antiemetic, Nighttime Sleep-Aid, and Stimulant OTC drug products were reopened for a 5-month period for the submission of new data and 2 additional months for the submission of comments (see 44 FR 61609; October 26, 1979). The agency also subsequently accepted into the administrative records all data on ingredients covered by the published TFM's that had been previously submitted outside of the periods when the administrative records were open (see 45 FR 18398–99; March 21, 1980). Substantial amounts of data have been submitted for these categories of drugs. Only extraordinary circumstances would warrant reopening of the administrative record for any category of drugs, and FDA will make that determination on a case-by-case basis. The tentative order on OTC emetic drug products published in the **Federal Register** of September 5, 1978 (43 FR 39544) contained no Category II or III ingredients or other conditions. Therefore, FDA sees no need to reopen the administrative record for this category of drugs.

12. One comment said that, based on the language used by the agency to justify holding the administrative record open for 14 months following a tentative final monograph, it was clear that the time period was intended to permit companies to submit new evidence of safety and effectiveness to justify continued marketing of a drug, not to simplify the administrative processes of finalizing the monograph. The comment said that the time period merely reduces the 2 to 5 years manufacturers previously had to conduct testing and submit safety and effectiveness data to FDA to 14 months. The comment argued that FDA's action clearly is not in accord with the court's order in *Cutler* because the court's decision was not based on the reasonableness of the time period allowed for establishment of safety and efficacy by new evidence, but was based on the lack of statutory authority allowing the Commissioner to permit continued marketing of a drug that has not been established as safe and effective. Thus, according to the comments, merely reducing the time period during which marketing is allowed fails to bring the regulatory scheme into compliance with the court's order and the statutory requirement, despite any assertions of administrative convenience made by FDA.

As discussed in the response to comment 6 above, and in the preamble to the proposed rule, the agency must complete certain scientific and administrative reviews and evaluations before issuing a final rule. The agency believes that permitting manufacturers to take advantage of this same time period for the submission of new data without petitioning to reopen the administrative record will simplify the agency's administrative tasks, will not delay the overall OTC drug review process, and is consistent with the court's order in *Cutler*.

13. One comment stated that to permit FDA to reclassify a claim or ingredient from Category I to Category III without affording a grace period of at least 3 years for the collection of data to upgrade the status would impose a distinctly unfair burden on industry. Therefore, the comment suggested that at least 3 years should be provided for the collection of efficacy data to upgrade an ingredient or claim to Category I in those instances where: (1) the Panel recommended classification as Category I, but the agency disagrees and so states in publishing a panel's recommendations; (2) the Panel recommended Category I status, but the agency disagrees and assigns a Category III designation in the tentative final monograph; and (3) the tentative final monograph designates Category I, but FDA intends to assign Category III status in the final monograph.

FDA believes that the situations posited by the comment will rarely occur. Further, if the agency does disagree with the Panel's classification of an ingredient in Category I, and announces that disagreement at the time the Panel Report is published, the manufacturer will have as much notice as it would had the Panel classified the ingredient in Category III. Thus, there should be adequate time for any necessary studies to be completed before the time that the administrative record closes.

FDA recognizes that an agency reclassification of a Category I ingredient to Category III in the tentative final monograph would present a specialized problem in that industry would have only 12 months to complete testing and submit the data to the agency. In such cases, the FDA Bureau of Drugs would ordinarily notify industry through the system of informal communications explained in the notice

that is discussed under comment 4 above and that is published elsewhere in this issue of the **Federal Register** as soon as it has reached a tentative decision to request the Commissioner to reclassify the ingredient in question into Category III in the tentative final monograph, so that testing could be initiated as soon as possible.

The proposed OTC procedural regulation stipulated that data submitted after the closing of the administrative record following publication of the tentative final monograph would be considered only after publication of a final order as a petition to amend the monograph (45 FR 31422, 31425). Section 330.10(a)(7)(v) (21 CFR 330.10(a)(7)(v)) has been amended to permit exceptions if good cause is shown, such as when there has been an agency reclassification of an ingredient from Category I to Category III in the TFM. Ordinarily, data submitted after the closing of the administrative record will not be reviewed until after publication of the final monograph. The revised regulation permits interested persons to petition the agency to reopen the administrative record before publication of a final monograph if they believe that there are exceptional grounds for the Commissioner to exercise the Commissioner's discretion to reopen the record.

Should FDA decide, based on comments to the TFM or new data and information, that a Category I ingredient should be reclassified to nonmonograph status in the final monograph, such an ingredient will be subject to regulatory action as specified in that document. It is the agency's view that such reclassification will occur only on the basis of unusually clear evidence that an ingredient cannot be generally recognized as safe and effective. Therefore, it would not be appropriate in that situation to defer regulatory action pending submission of new data.

14. One comment urged that the agency approve promptly all studies previously submitted while the administrative record was considered open, which justify the upgrading of ingredients and claims from Category III to Category I. The comment argued that any further delay in approving these studies will cause sponsors who are uncertain of the future status of the products involved to make unnecessary expenditures of time, effort, and money.

The agency advises that the policy statement, published elsewhere in this issue of the **Federal Register**, provides a mechanism through which manufacturers may contact the agency to determine the status of data previously submitted before initiating further studies. FDA believes that the opportunity for communications described in the notice will aid in reducing unnecessary expenditures of time, money, and effort by manufacturers.

15. Two comments referred to the **Federal Register** notices of March 21, 1980 (45 FR 18398). In those notices, FDA accepted into the administrative record data submitted as comments on proposed and tentative final monographs after the closing of the administrative record. FDA announced that it was treating the comments as petitions to reopen the various administrative records and was granting those petitions. The comment interpreted this revised Category III regulation to state that such data, having been accepted into the administrative record by virtue of the March 21 notices, will be reflected in tentative final and final monographs in the same way as data submitted during the original comment period. The comment asked whether this interpretation is correct.

The comment has interpreted the regulation correctly.

Category II Conditions

16. Two comments on proposed § 330.10(a)(7)(ii) noted that any given ingredient in the OTC drug review may have more than one indication for use, may be reviewed by more than one panel, and may be categorized differently by the panels. The comments said that if FDA chooses to expedite regulatory action against an ingredient by publishing a separate tentative order for that ingredient, FDA should confine such action to the ingredient when it is used for the particular disfavored indication.

The agency advises that any tentative order that FDA publishes for an ingredient classified by a panel in Category II and for which no substantive comments in opposition to the panel report or no new data are submitted will be confined to the use of that ingredient for specific indications within a specific category of drugs.

17. One comment focused on FDA's proposal to issue separate "early" tentative final and final orders on ingredients recommended by a panel as Category II, for which the agency does not receive substantive comments in opposition to the panel report or new data and information. The comment contended that FDA should act similarly for ingredients recommended by a panel as Category I for which no comments are received disputing that status.

The agency advises that the reason for expediting completion of the OTC drug panel review for ingredients recommended by a panel as Category II and for which the agency does not receive substantive comments in opposition to the panel report or new data and information is to remove from the market as quickly as possible drug products containing ingredients not generally recognized as safe and effective. Substantive comments are those that warrant response by the agency through a TFM, with an opportunity for objections, and the term does not include comments that are merely conclusory or rely on legally irrelevant or inconsequential grounds for support. This action clearly serves the public interest. OTC drug products containing ingredients recommended as Category I by a panel for which no comments are received disputing that status will retain that status at the final monograph stage unless new information is developed indicating that the ingredient ought not to be included in the monograph. Therefore, the ingredient will remain on the market. Agency resources can be more efficiently used in expediting those parts of the OTC drug review that are necessary for the protection of the public health.

The Commissioner may, of course, continue to act, without observing all of the procedures governing the full OTC review, when the Commissioner finds it necessary to do so. Thus, the Commissioner may issue a rule through notice-and-comment procedures, without following the usual OTC review procedure, or take other regulatory action, when the Commissioner finds it necessary to protect the public from a significant safety risk posed by an OTC product. On a number of occasions the agency has used only notice-and-comment procedures in issuing rules to deal with problems needing prompt action posed by an OTC product, e.g., 21 CFR 310.508 (halogenated salicylanilides), 21 CFR 310.525 (sweet spirits of nitre).

OTC Drug Review Classification Terminology

18. One comment agreed with the proposed revisions and stated that the terms "monograph conditions" or "nonmonograph conditions" will be fair and equitable once the rule has been enforced for some period of time. The comment expressed concern, however, that during the early stages following implementation of this new policy, inequities may develop because it is likely that all previous Category II and Category III products will be treated as "nonmonograph conditions." Thus the old distinctions between Category II and

III will no longer be operative, and Category III products will be tainted in the eyes of the consumer by their association with Category II products. The comment suggested that during the next several years, until the revised policy has had time to become operative, FDA should establish a special category for products currently in Category III, on which testing is being done, so that these products will not be treated as "nonmonograph conditions."

The agency has carefully considered the comment and concluded that no revision of the regulation as proposed is necessary. The agency believes that it is appropriate to describe as "nonmonograph conditions" all those conditions that have not been found to be generally recognized as safe and effective and thus not included in the monograph. All "nonmonograph conditions" are subject to regulatory action; however, FDA's enforcement policy recognizes that different nonmonograph conditions pose varying public health problems. Accordingly, FDA's enforcement policy gives higher priority to those conditions, ingredients, or claims that pose the greatest risk to the consumer.

19. One comment suggested retaining the terms "Category I" and "Category II" after publication of the final monograph. Because of its usage over the past 8 years, the OTC drug industry understands that Category II products are illegal. Further, because Judge Sirica held the sale of Category III products to be illegal, all products that are not generally recognized as safe and effective should be treated equally and should be classified in Category II. The comment argued that substituting the terms "monograph" and "nonmonograph" conditions could have the effect of suggesting that "nonmonograph" conditions are not necessarily illegal. Another comment objected, without stating a reason, to the agency's proposed terms "monograph conditions," and "nonmonograph conditions."

The agency does not agree that the term "nonmonograph condition" in any way suggests that such conditions may not be illegal. Only OTC drug products meeting the conditions of a monograph or having an approved new drug application may be legally marketed. Therefore, any OTC drug product containing a condition not included in a monograph will be subject to regulatory action unless the drug product has an approved new drug application. The agency considers the term "nonmonograph condition" to be appropriate and not to be misleading.

Regulatory Policy

20. One comment said that the enforcement priorities proposed for drugs that fail to meet the monograph conditions are not rationally justified. Another comment objected both to the order of the enforcement priorities and to their disclosure, but would not object to FDA's stating that it will place special emphasis on products which present health hazards or on the most frequently prescribed products. The comment also argued that FDA should proceed vigorously against any manufacturer who markets an ineffective drug product, regardless of whether the drug product was formerly in Category II or Category III, and regardless of whether a petition to amend the monograph or new drug application is pending. Both comments argued that the effect of publishing an enforcement priority list will be to encourage manufacturers of a product with a lower enforcement priority to continue to market that product on the assumption that the agency will not have the resources to proceed against them. One comment said that assigning first priority to "products that present a potential health hazard" and then also listing those categories of conditions having lower priorities imply that products in these latter categories do not present "a potential health hazard." The comment argued that this is inaccurate because any product not established as safe and effective presents a potential health hazard. When the degree of that hazard is determined to be substantial, according to the comment, FDA ought to assign it first priority. The comment recommended that this provision of the proposed rule be deleted or replaced with a priority listing that is fully justified and that leaves enough flexibility to avoid signaling areas of nonenforcement.

The enforcement priorities are not of the OTC procedural regulations. They were included in the preamble to the May 16, 1980, proposed rule only to advise the public that FDA has developed a broad policy of taking regulatory action first against those products that most affect the public health, commensurate with agency resources and basic principles of equity. FDA agrees with the comment that any product that presents a potential health hazard, whether caused by safety or effectiveness problems, should have the highest priority. That is the system proposed by FDA, and explained in the preamble to the proposed rule.

21. One comment believed it unwise to set enforcement priorities when so few final monographs have been published, because it is likely that important considerations may have been overlooked. For example, the comment said that, after safety, the next most determinative factor should be the extent of exposure of the public to the drug product in question, and that FDA should place special emphasis on the most frequently used drugs. Yet this factor does not appear in the enforcement priorities, and there may be other factors which will come to light only when a substantial number of final monographs have been published.

FDA emphasizes that this policy is not necessarily a final and comprehensive statement of FDA's enforcement posture with respect to all aspects of OTC drug compliance. The policy is subject to change, depending on various factors existing in the marketplace. FDA agrees with the comment that the extent of public exposure to a drug ought to be a factor in assigning enforcement priorities to OTC drug products. The enforcement priorities will be modified accordingly. As discussed in the proposal, FDA may further modify or amplify the enforcement policy at any time, or take regulatory action outside the priorities listed should such action be deemed necessary.

22. One comment on FDA's enforcement policy questioned the accuracy and legality of FDA's statement that after a final monograph is issued, only OTC drug products meeting the conditions of the monograph or having an approved new drug application may be legally marketed. The comment argued that if data submitted to the agency after closing of the administrative record following publication of a tentative final monograph show that a particular drug is in fact generally recognized as safe and effective and not misbranded, it would be preposterous for FDA to argue that the drug was technically illegal simply because it had not been approved in FDA's final monograph. The comment further argued that if new data became available after FDA closes the record in an OTC drug review rulemaking proceeding, FDA's monograph, issued without consideration of the new data, would not be controlling with respect to the significance of the new data. Instead, in any attempted FDA enforcement action, there would be *de novo* judicial review of the significance of the new data. The comment cited *Citizens to Preserve Overton Park* v. *Volpe*, 401 U.S. 402, 415 (1971) saying "* * * there may be independent judicial fact finding when issues that were not before the agency

are raised in a proceeding to enforce nonadjudicatory agency action."

While the comment is correct that issues not before the agency in an administrative proceeding may be litigated in court, such *de novo* judicial review is time consuming and wasteful. Avoiding such litigation was one of the reasons for establishing the OTC Drug Review as a rulemaking proceeding. The OTC drug review process establishes an orderly administrative procedure for determining those conditions that are generally recognized as safe and effective. Once a final monograph is effective, any OTC drug product not in compliance with the monograph or not covered by an approved new drug application is subject to regulatory action. Industry is urged to conduct the necessary testing and to submit data promptly to FDA within the time periods provided by the OTC drug review procedural regulations in order to upgrade an ingredient to monograph status at the final monograph stage, thus obviating the possibility of such litigation.

23. One comment argued that enforcement priority 6 (products that contain an ingredient or claim excluded from the monograph because of insufficient information and for which a full and complete petition to amend the monograph is pending before the agency) and priority 7 (products that contain a nonmonograph ingredient or claim for which there is a pending new drug application (NDA) before the agency) will, if retained, encourage manufacturers to file frivolous petitions and NDA's in order to avoid enforcement by FDA.

The agency disagrees with the comment. Petitions and NDA's pending before the agency will be given a preliminary review by FDA upon receipt to ensure that they are full and complete. The agency expects to use its available resources to the extent possible to ensure that products containing nonmonograph ingredients or indications are removed from the market.

In accordance with Executive Order 12291, FDA has determined that neither this final rule nor the related notice of policy statement published elsewhere in this issue of the **Federal Register** constitutes a major rule. This determination is set forth in the Threshold Assessment under Executive Order 12291 for the final rule revising OTC procedural regulations relating to Category III and for the accompanying policy statement. A copy of this document is on file with the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701(a), 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055 (21 U.S.C. 321, 352, 355, 371(a))) and 21 CFR 5.11 and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), (formerly 5.1; see 46 FR 26052; May 11, 1981). Part 330 is amended in § 330.10 by revising paragraph (a) (7), (9), (10), and (12) and by deleting paragraph (a)(13) as follows:

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

* * * * *

(a) * * *

(7) *Tentative final monograph.* (i) After reviewing all comments, reply comments, and any new data and information, the Commissioner shall publish in the **Federal Register** a tentative order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. Within 60 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. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(ii) The Commissioner may 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, and for which no substantive comments in opposition to the panel report or new data and information were received by the Food and Drug Administration pursuant to paragraph (a)(6)(iv) of this section. Within 60 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. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(iii) Within 12 months after publishing a tentative order pursuant to paragraph (a)(7)(i) of this section, any interested person may file with the Dockets Management Branch, Food and Drug Administration, new data and information to support a condition excluded from the monograph in the tentative order.

(iv) Within 60 days after the final day for submission of new data and information, comments on the new data and information may be filed with the Dockets Management Branch, Food and Drug Administration.

(v) New data and information submitted after the time specified in this paragraph but prior to the establishment of a final monograph will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final monograph has been published in the **Federal Register** unless the Commisisoner finds that good cause has been shown that warrants earlier consideration.

* * * * *

(9) *Final monograph.* After reviewing the objections, the entire administrative record including all new data and information and comments, and considering the arguments made at any oral hearing, the Commissioner shall publish in the **Federal Register** a final order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. The monograph shall become effective as specified in the order.

(10) *Administrative record.* (i) All data and information to be considered in any proceeding pursuant to this section shall be submitted in response to the request for data and views pursuant to paragraph (a)(2) of this section or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section or submitted to the Dockets Management Branch as part of the comments during the 90-day period and 30-day rebuttal comment period permitted pursuant to paragraph (a)(6) of this section or submitted to the Dockets Management Branch during the 12-month period or as part of the comments during the 60-day period permitted pursuant to paragraph (a)(7) of this section.

(ii) The Commissioner shall make all decisions and issue all orders pursuant to this section solely on the basis of the

administrative record, and shall not consider data or information not included as part of the administrative record.

(iii) The administrative record shall consist solely of the following material: All notices and orders published in the **Federal Register**, all data and views submitted in response to the request published pursuant to paragrah (a)(2) of this section or accepted by the panel during its deliberations pursuant to paragraph (a)(3) of this section, all minutes of panel meetings, the panel report(s), all comments and rebuttal comments submitted on the proposed monograph and all new data and information submitted pursuant to paragraph (a)(6) of this section, all objections submitted on the tentative final monograph and all new data and information and comments submitted pursuant to paragraph (a)(7) of this section, the complete record of any oral public hearing conducted pursuant to paragraph (a)(8) of this section, all other comments requested at any time by the Commissioner, all data and information for which the Commissioner has reopened the administrative record, and all other material that the Commissioner includes in the administrative record as part of the basis for the Commissioner's decision.

* * * * *

(12) *Amendment of monographs.* (i) The Commissioner may propose on the Commissioner's own initiative to amend or repeal any monograph established pursuant to this section. Any interested person may petition the Commissioner for such proposal pursuant to § 10.30 of this chapter. The Commissioner may deny the petition if the Commissioner finds a lack of safety or effectiveness employing the standards in paragraph (a)(4) of this section (in which case the appeal provisions of paragraph (a)(11) of this section shall apply), or the Commissioner may publish a proposed amendment or repeal in the **Federal Register** if the Commissioner finds general recognition of safety and effectiveness employing the standards in paragraph (a)(4) of this section. Any interested person may, within 60 days after publication of the proposed order in the **Federal Register**, file with the Dockets Management Branch, Food and Drug Administration, written comments in quadruplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed in the Dockets Management Branch between the hours of 9 a.m. and 4 p.m., Monday through Friday. After reviewing the comments, the Commissioner shall publish a final order amending the monograph established under the provisions of paragraph (a)(9) of this section or withdraw the proposal if comments opposing the amendment are persuasive. A new drug application may be submitted in lieu of, or in addition to, a petition under this paragraph.

(ii) A new drug application may be submitted in lieu of a petition to amend the OTC drug monograh only if the drug product with the condition that is the subject of the new drug application has not been marketed on an interim basis (such as under the provisions of paragraph (a)(6)(iii) of this section), all clinical testing has been conducted pursuant to a new drug application plan, and no marketing of the product with the condition for which approval is sought is undertaken prior to approval of the new drug application. The Food and Drug Administration shall handle a new drug application as a petition for amendment of a monograph, and shall review it on that basis, if the provisions of this paragraph preclude approval of a new drug application but permit the granting of such a petition.

* * * * *

Effective date. This regulation shall be effective November 30, 1981.

(Secs. 201, 502, 505, 701(a), 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055 (21 U.S.C. 321, 352, 355, 371(a)))

Dated: July 7, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: September 8, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

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