DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 79N-0368]

Cholecystokinetic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) cholecystokinetic drug products (products that cause contraction of the gallbladder during diagnostic gallbladder studies) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and the public comment on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by October 25, 1982. Written comments on the agency's economic impact determination by December 22, 1982.

ADDRESS: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In the Federal Register of February 12, 1980 (45 FR 9286) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cholecystokinetic drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by May 12, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by June 11, 1980.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

The advance notice of proposed rulemaking, which was published in the Federal Register of February 12, 1980 (45 FR 9286), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC cholecystokinetic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC cholecystokinetic drug products.

In response to the advance notice of proposed rulemaking, one pharmaceutical company submitted a comment. Copies of this comment are also on public display in the Dockets Management Branch.

This proposal would amend Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations in Part 357 (as set forth elsewhere in this issue of the Federal Register) by adding Subpart C. This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC cholecystokinetic drug products as modified on the basis of the comment received and the agency's independent evaluation of the Panel's report. Some modifications have been made for clarity and are reflected in the tentative final monograph.

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The revised regulations provide in § 330.10(a)(7)(iii) for a 12-month period to submit data and information to support a condition excluded from the monograph in the tentative final order. In the case of cholecystokinetic drug products, the only condition considered was included in the monograph. Therefore, the agency concludes that the usual 12-month comment period would serve no purpose in developing a final monograph for OTC cholecystokinetic drug products.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC cholecystokinetic drug products (published in the Federal Register of February 12, 1980 (45 FR 9286)), the agency had suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the Federal Register. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the Federal Register. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and have their products in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

The "OTC Volume" cited in this document refers to the submission made by an interested person pursuant to the call-for-data notices published in the Federal Register of November 16, 1973 (38 FR 31696) and in the Federal Register of August 27, 1975 (40 FR 38179). The volume is on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusion on the Comment

One comment stated that the only use for cholecystokinetic drug products is to cause contraction of the gallbladder during cholecystography, and thus they are always dispensed or under the supervision of the physician requesting the cholecystogram. The comment concluded that thest drugs, therefore, are not OTC drugs and that the establishment of an OTC drug monograph for these products is inappropriate and not in the best interest of the patients for whom these products are intended.

The agency agrees with the comment that the product should be used under the supervision of the physician. However, the agency points out that the Panel concluded that an aqueous emulsion of corn oil, the only ingredient it reviewed, is safe and effective for use as an OTC cholecystokinetic drug product. Because patients may be advised by a physician to obtain this drug and use it at a given time in preparation for the diagnostic procedure, the agency agrees with the Panel and believes that the status of this product as an OTC drug will benefit consumers by assuring its convenient availability when it is needed. The labeling proposed for the product in this tentative final monograph is clear and specific, adequately informs the consumer of the intended use of the product, and makes misuse unlikely. Therefore, the agency believes that this drug product can be marketed OTC and that establishing this tentative final monograph for OTC cholecystokinetic drug products is not adverse to the interests of those consumers for whom such products are intended.

II. The Agency's Tentative Adoption of the Panel's Report

1. In § 357.250(a), the Panel recommended a statement of identity which identifies the product as a "cholecystokinetic." The agency believes that the word cholecystokinetic is not well understood by consumers and that the use of the words "gallbladder diagnostic agent" as the statement of identity would result in a better understanding of the intended OTC use of the product. The agency is revising the statement of identity in § 357.250(a) accordingly.

2. In § 357.250(b)(1), the Panel recommended an indication that designates the product's use as "For the contraction of the gallbladder during cholecystography." The agency believes that the word "cholecystography" is not well understood by consumers and is, therefore, substituting the words "diagnostic gallbladder studies" for the word "cholecystography" in § 357.250(b)(1) in the tentative final monograph. The agency also believes that the Panel's indication in § 357.250(b)(2), which states that the product is used "for visualization of biliary ducts during cholecystography," would not be well understood by consumers, and that the modified indication in § 357.250(b)(1) in this tentative final monograph is adequate to inform consumers of the intended OTC use of the product. However, the agency believes that the information contained in § 357.250(b)(2) should be provided to health professionals, and is moving this indication to a new professional labeling section in the tentative final monograph. In addition, the agency has reviewed the data submitted to the Panel (Ref. 1) and has determined that the usual dose of 50 percent corn oil emulsion for cholecystography is 60 milliliters (mL). The data indicate that the 60-mL dose should be taken 20 minutes before a postcontraction biliary x-ray is scheduled. The agency believes that, because these products are only used when directed by a physician, dosing information should also be provided in the professional labeling. Thus, the agency is proposing professional labeling as new § 357.280, which will include the following indication and dosage:

(a) *Indication.* "For visualization of biliary ducts during cholecystography."

(b) *Dosage.* Oral dosage is 60 milliliters of a 50-percent aqueous emulsion of corn oil taken 20 minutes before postcontraction biliary x-ray.

Reference

(1) OTC Volume 170045.

3. In § 357.250(c)(1), the Panel recommended the use of the phrase "* * * when instructed by a physician." Believing that the word "doctor" is more commonly used and better understood by consumers, the agency is substituting "doctor" for "physician" in this section of the tentative final monograph. This change is made as part of a continuing effort to achieve OTC labeling language that is simple, clear, and accurate, in keeping with § 330.10(a)(4)(v), (21 CFR 330.10(a)(4)(v)), which states in part, "Labeling * * * shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use." If the word "doctor" is adopted in the final monograph, the agency will use this language in other final monographs and other applicable OTC drug regulations and will propose amendments to those regulations accordingly. Public comment on this proposed change in labeling language is invited.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Public Law 96-354). Specifically, the proposal would require only a small amount of relabeling, and any reformulation, if necessary, would be minor. Therefore, the agency concludes that the proposed rule is not a major rule as defined in

Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC cholecystokinetic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC cholecystokinetic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on cholecystokinetic drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the Federal Register of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 357

OTC drugs: Anthelmintics, Cholecystokinetics.

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 357 (as set forth elsewhere in this issue of the Federal Register) by adding new Subpart C, to read as follows:

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Subpart C—Cholecystokinetic Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

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Subpart C—Cholecystokinetic Drug Products

§ 357.201 Scope.

(a) An over-the-counter cholecystokinetic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart in addition to each of the general conditions established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 357.203 Definition.

As used in this part:

Cholecystokinetic drug product. A drug product that causes contraction of the gallbladder and is used during the course of diagnostic gallbladder studies (cholecystography).

§ 357.210 Cholecystokinetic active ingredient.

The active ingredient of the product is a 50-percent aqueous emulsion of corn oil.

§ 357.250 Labeling of cholecystokinetic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "gallbladder diagnostic agent."

(b) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indication" that is limited to the phrase "For the contraction of the gallbladder during diagnostic gallbladder studies."

(c) *Warnings.* [Reserved]

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions":

(1) "Take only when instructed by a doctor."

(2) "Shake well before using."

§ 357.280 Professional labeling.

The labeling provided to health professionals (but not to the general public) may contain the following information for products containing a 50-percent aqueous emulsion of corn oil:

(a) *Indication.* "For visualization of biliary ducts during cholecystography."

(b) *Dosage.* Oral dosage is 60 milliliters of a 50-percent aqueous emulsion of corn oil taken 20 minutes before postcontraction biliary x-ray.

Interested persons may, on or before October 25, 1982 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 22, 1982. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be acccompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on October 25, 1982. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: June 15, 1982.

Arthur Hull Hayes, Jr.,
Commissioner of Food and Drugs.

Dated: July 13, 1982.

Richard S. Schweiker,
Secretary of Health and Human Services.

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21 C. . . Part 341

[Docket No. 76N-052C]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Over-the-Counter Anticholinergic Drug Products and Expectorant Drug Products; Notice of Proposed Rulemaking; Extension of Time for Comments, Objections, or Requests for Oral Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking; extension of period for comments, objections, or requests for oral hearing.

SUMMARY: The Food and Drug Administration (FDA) is extending the period for comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs for the notice of proposed rulemaking to establish conditions for the safety, effectiveness, and labeling of over-the-counter (OTC) anticholinergic drug products and expectorant drug products. This action is being taken in response to a request to allow more time for interested persons to compile and submit data on existing studies on the effectiveness of guaifenesin, a Category III expectorant active ingredient, and to consult experts so that more informed comments may be submitted to FDA.

DATE: Written comments, objections, or requests for oral hearing by November 8, 1982.

ADDRESS: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In the Federal Register of July 9, 1982 (47 FR 30002), FDA issued a notice of proposed rulemaking to establish conditions for the safety, effectiveness, and labeling of anticholinergic drug products and expectorant drug products for OTC human use. This notice of proposed rulemaking, which was based on the agency's evaluation of recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, and public comments on those recommendations, is part of the ongoing review of OTC drug products conducted by the agency. Interested persons were given until September 7, 1982 to submit written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the notice of proposed rulemaking.

In response to the proposal, A. H. Robins Co. requested a 60-day extension of the time in which to submit comments, objections, or requests for oral hearing in order to allow adequate time for the company to compile and submit data on existing studies on the effectiveness of guaifenesin. These data include human and animal studies and a recent study conducted in Italy to demonstrate the effectiveness of guaifenesin in humans using the objective measurements recommended to A. H. Robins Co. by FDA. The company stated that, as soon as possible after the submission of these data, it plans to meet with FDA to determine if the agency considers these data satisfactory to prove the effectiveness of guaifenesin, or if additional studies will be required. The company added that if the agency concludes that the effectiveness of guaifenesin has not been proven, then it will file comments, objections, and a request for a hearing. The company stated that it plans to contact experts to evaluate the new data and the data previously submitted to FDA and pointed out the difficulty of contacting and consulting with such experts during the summer months.

FDA has carefully considered the request. The agency believes that the studies described in the request may be of assistance in establishing the effectiveness of guaifenesin as an OTC expectorant drug product and may obviate the need for further comments or objections in support of guaifenesin. FDA considers the request to be in the public interest because there currently are no Category I expectorant drug products. The agency therefore considers a general extension of 60 days to be appropriate. Accordingly, the period for comments, objections, or requests for oral hearing by any interested person is extended to November 8, 1982. The agency points out that this extension will not in any way extend the time for final action by the agency on the proposed regulation because the July 11, 1983 date for the submission of new data remains unchanged. Comments may be seen in the Dockets Management Branch, Food and Drug Administration (address above), between 9 a.m. and 4 p.m., Monday through Friday.

Dated: August 23, 1982.

Joseph P. Hile,