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; Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing 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 final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on cholecystokinetic drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: June 11, 1984.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFN-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 (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for cholecystokinetic drug products was published in the **Federal Register** of August 24, 1982 (47 FR 37068). Interested persons were invited to file by October 25, 1982 written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation. Interested persons were invited to file by December 22, 1982 written comments on the agency's economic impact determination. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC cholecystokinetic drug products.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September 29, 1981; FR 47730.) The revised regulations now 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 order. In the case of cholecystokinetic drug products, the only condition considered was included in the monograph. Therefore, in the preamble to the proposed regulation the agency indicated that the usual 12-month comment period would serve no purpose in developing a final monograph for OTC cholecystokinetic drug products (47 FR 37068).

Although it was not required to do so under *Cutler*, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC cholecystokinetic drug products (47 FR 37068), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective on June 11, 1984. 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 relabeled 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 response to the proposed regulation on OTC cholecystokinetic drug products, comments were received from a College of Pharmacy and a drug manufacturer. Copies of these comments are on public display in the Dockets Management Branch (address above).

I. The Agency's conclusions on the Comments

1. One comment disagreed with the agency's proposed substitution of the word "doctor" for "physician" in § 357.250(d)(1) of the tentative final monograph. The comment stated that because "physician" is a term that is recognized by people of all ages and social and economic levels, there is no need for such a costly change providing absolutely no benefits. The comment further contended that "physician" is a more accurate term, whereas "doctor" is a broad term that could confuse and mislead the lay person into taking advice on medication from persons other than medical doctors, such as optometrists, podiatrists, and even chiropractors.

The agency recognizes that the term "doctor" is not a precise synonym for the word "physician," but believes that the terms are frequently used interchangeably by many consumers. Although the agency has proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in an effort to simplify OTC drug labeling, the agency has determined, based on comments received to these proposals, that final monographs and other applicable OTC drug regulations should give manufacturers the option of using either the word "physician" or the word "doctor." This final monograph includes that option.

2. One comment noted that the tentative final monograph permits dosage directions only in professional labeling and indicated that such information should be included in product container labeling. The comment argued that not including

dosage information on product labeling is contrary to the Federal Food, Drug, and Cosmetic Act, which requires OTC drug labeling to contain information adequate to permit a consumer to use a drug properly. The comment added that dosage information on product labeling is useful to both consumers and doctors and that not allowing this type of information will require doctors to issue a prescription to provide the dosage directions, thus increasing the possibility of error or misunderstanding. Finally, the comment cited marketing experience of a cholecystokinetic drug product containing dosage directions on product labeling, indicating that this product has been sold for 20 years without reported confusion, misuse, or consumer or professional concern.

The agency agrees with the comment that the labeling of OTC cholecystokinetic drug products should include dosage information. The agency included dosage information only in professional labeling in the tentative final monograph because these products are used only when directed by a doctor (47 FR 37069). However, the agency recognizes that dosage information can also be a useful supplement to a doctor's instructions. Accordingly, the agency is moving the dosage information contained in the professional labeling section of the tentative final monograph to the OTC labeling section of this final monograph. This information has been modified slightly to read as follows: Oral dosage is 60 milliliters 20 minutes before diagnostic gallbladder x-ray or as directed by a doctor.

II. The Agency's Final Conclusions on OTC Cholecystokinetic Drug Products

Based on the available evidence, the agency is issuing a final rule establishing monograph conditions under which OTC cholecystokinetic drug products are generally recognized as safe and effective and not misbranded. Any drug product marketed for use as an OTC cholecystokinetic that is not in conformance with the monograph (21 CFR Part 357, Subpart C) will be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and may not be marketed for this use unless it is the subject of an approved new drug application.

During the course of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or, after issuance of final monographs, through petitions to amend monographs under § 330.10(a)(12).

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by the Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA conducted an open public forum on September 29, 1982 at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544). Details of the hearing were announced in a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002). The agency's decision on this matter will be announced following conclusion of its review of the material presented at the hearing.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 37070). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC cholecystokinetic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC cholecystokinetic drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

List of Subjects in 21 CFR Part 357

OTC drugs, Cholecystokinetics.

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), Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended by adding new Part 357 to read as follows:

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

Subpart A—[Reserved]

Subpart B—[Reserved]

Subpart C—Cholecystokinetic Drug Products

Sec.

357.201 Scope.
357.203 Definition.
357.210 Cholecystokinetic active ingredient.
357.250 Labeling of cholecystokinetic drug products.
357.280 Professional labeling.

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).

Subpart A—[Reserved]

Subpart B—[Reserved]

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 subpart:

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."

(3) Oral dosage is 60 milliliters 20 minutes before diagnostic gallbladder x-ray or as directed by a doctor.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 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: *Indication.* "For visualization of biliary ducts during cholecystography."

Effective date. This monograph is effective on June 11, 1984.

(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).)

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

Dated: May 18, 1983.

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