DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 76N-052C]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Anticholinergic Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any anticholinergic drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective, is misbranded, and is subject to regulatory action unless it has an approved new drug application (NDA). (Anticholinergics are drugs used in cough-cold products for the relief of excessive secretions of the nose and eyes, symptoms which are commonly associated with hay fever, allergy, rhinitis, and the "common cold" (cold)). 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 anticholinergic drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: November 10, 1986.

FOR FURTHER INFORMATION CONTACT: William E. Gilberston, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 9, 1976 (41 FR 38312), 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 cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on 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 rule, in the form of a tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is being issued in the following segments: anticholinergics and expectorants, bronchodilators, antitussives, nasal decongestants, antihistamines, and combinations. The first segment, the tentative final monograph for anticholinergic drug products and expectorant drug products, was published in the **Federal Register** of July 9, 1982 (47 FR 30002). Interested persons were invited to file by September 7, 1982, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by November 8, 1982. New data could have been submitted until July 11, 1983, and comments on the new data until Septmber 9, 1983.

In a notice published in the **Federal Register** of August 27, 1982 (47 FR 37934), the agency advised that it had extended the period for comments, objections, or requests for oral hearing for OTC anticholinergic drug products and expectorant drug products. The notice allowed the period for comments, objections, or requests for oral hearing to be extended to November 8, 1982.

The agency's final rule in the form of a final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is also being published in segments. Final agency action on antichlolinergic drug products occurs with the publication of this document. The expectorant segment will be the subject of a separate **Federal Register** document.

In the preamble to the agency's proposed rule on OTC anticholinergic drug products (47 FR 30002), the agency stated that no anticholineric active ingredients had been found to be generally recognized as safe and effective and not misbranded, but that Category I labeling was being proposed in that document in the event that data were submitted that resulted in the upgrading of any ingredients to monograph status in the final rule. In this final rule, no anticholinergic ingredient has been determined to be generally recognized as safe and effective for cough-cold use. Therefore, the labeling for anticholinergics in § 341.70 of the proposed rule is not included in this document. This final rule declares products containing anticholinergic active ingredients for cough-cold use to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which a new drug application approved under section 505 of the act (21 U.S.C. 355) and 21 CFR Part 314 is required for marketing. In the absence of an approved new drug application, products containing these drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). This final rule amends 21 CFR Part 310 to include anticholinergics for cough-cold use by adding to Subpart E new § 310.533 (21 CFR 310.533). The inclusion of anticholinergic drugs for OTC cough-cold use in Part 310 is consistent with FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, and 310.526.) If, in the future, any ingredient is determined to be generally recognized as safe and effective as an OTC anticholinergic for cough-cold use, the agency will promulgate an appropriate regulation at that time.

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, 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).

In the proposed rule for OTC anticholinergic drug products (47 FR 30003), the agency advised that it was not aware that any anticholinergic ingredients were being tested and that products containing anticholinergic ingredients may have to be reformulated. The agency has established a period of 12 months after the date of publication of the final rule in the **Federal Register** for reformulation

of products. Although the agency is now aware that one manufacturer has expressed interest in testing anticholinergics and has submitted a protocol, the results of a study have not been submitted to the agency for evaluation. Therefore, anticholinergic drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). On or after November 10, 1986, no OTC anticholinergic-containing drug products that are subject to this final rule 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 NDA.

In response to the proposed rule on OTC anticholinergic drug products, one manufacturer, two drug manufacturer associations, one health care professional, and one health care professional society submitted comments. Copies of the comments received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments on Anticholinergic Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3. of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharamaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).

2. One comment disagreed with the agency's statement that "no anticholinergic active ingredients have been determined to be generally recognized as safe and effective and not misbranded" (47 FR 30002). Arguing that the evidence to support the safety and effectiveness of these ingredients may not be conclusive, the comment stated that most of these drugs are not unsafe when used as directed by the manufacturers. The drugs may be effective in a "significant proportion of patients," the comment maintained, and it would be desirable to examine the physiologic and pharmacologic effects of these drugs to determine whether larger than recommended doses do have measurable beneficial or harmful effects in patients who claim that "standard" doses produce subjective benefits.

The agency's statement that "no anticholinergic active ingredients have been determined to be generally recognized as safe and effective and not misbranded" was a tentative conclusion based on a lack of adequate studies at that time to support the use of these drugs for their claimed effects. The data remain inadequate to upgrade any anticholinergic ingredient to a monograph condition.

In accordance with 21 CFR 310.533, which is being promulgated with the publication of this document, manufacturers may test nonmonograph anticholinergic ingredients to determine whether the Panel's recommended doses or even larger doses are effective. If the larger than recommended doses are not within a known safety range, additional safety studies will be needed.

3. In response to the agency's request for definitions of the term "anticholinergic" in lay language (47 FR 30004), one comment suggested that "anticholinergic" be defined as "a drug that acts upon those mechanisms in the damaged nose or lungs which lead to the production of excessive secretions so as to decrease their production thereby resulting in a drying effect." The comment also stated that the definition of anticholinergic drugs should mention the specific anticholinergic action from a pharmacologic or structural point of view.

The agency concludes that the definition offered by the comment for the term "anticholinergic" does not appear to be any clearer or more appropriate than that proposed by the agency in § 341.3 (47 FR 30009). By inviting public comment on definitions for "anticholinergic," the agency acknowledged the difficulty in defining this word in lay terms. In the tentative final monograph, the agency proposed §§ 341.3 and 341.70, which contain the definition of anticholinergic and the labeling for anticholinergic drugs, respectively. Because there are no safe and effective anticholinergic ingredients to be included in a final monograph, §§ 341.3 and 341.70 are not included in this document.

4. One comment stated that because there is a striking lack of data regarding the use of anticholinergic drugs in children, it is important to have research conducted to clarify the role of these agents in the care of children.

The agency agrees with the comment that there is a lack of data regarding the use of anticholinergic drugs in children. Because of this lack of data, the Panel consulted a committee of experts on pediatric drug therapy in order to determine pediatric dosages for OTC cough-cold drug ingredients. The Panel and the pediatric committee recommended that pediatric dosages based on age be allowed for those OTC drugs that had a wide margin of safety and for which adequate effectiveness data were available. The agency agrees that research to clarify the role of anticholinergics in the care of children should be conducted.

B. Comment on Anticholinergic Drug Products

5. One comment disagreed with the agency's tentative conclusion to classify atropine sulfate as an anticholinergic in Category III. The comment stated that marketing experience over a 20-year period with no adverse reactions traceable to atropine sulfate and favorable feedback from health professionals attest to the effectiveness of its combination drug products containing atropine sulfate. The comment submitted a proposed protocol, 7 references, and 161 testimonials in support of its request to classify atropine sulfate at a dose of 0.2 milligram (mg) or greater in Category I (Ref. 1). The comment added that its products are designed for use in industrial medical dispensaries where it is important to treat workers' colds with a drug that does not cause drowsiness and that forced removal of atropine sulfate from these products would not

only have a detrimental effect on the efficiency of workers, but would also result in substantial economic hardship to its company.

The agency evaluated the comment's proposed protocol for studying the effectiveness of atropine sulfate as an OTC anticholinergic and responded with a number of suggestions regarding that protocol (Ref. 2). The results of a study have not yet been submitted to the agency. Marketing experience and testimonials alone cannot be considered proof of effectiveness, but must be corroborated by clinical studies (see 21 CFR 330.10(a)(4)(ii)). The agency evaluated the seven references and determined that none of the studies can be used as supportive evidence for the effectiveness of atropine sulfate for use as an OTC anticholinergic to relieve excessive secretions of the nose and eyes associated with hay fever, allergy, and colds. Cullumbine et al. (Ref. 3) studied the safety and tolerance of higher doses of atropine sulfate in healthy volunteers. Murrin (Ref. 4) studied the dose-effect characteristics of atropine on depression of salivation. Mirakhur (Ref. 5) compared oral and intramuscular doses of atropine and measured the reduction of salivary secretions in normal adults. Joseph et al. (Ref. 6) compared the effect of oral and subcutaneous doses of atropine on salivary secretions in children undergoing tonsillectomy. Light et al. (Ref. 7) studied the effects of oral doses of 0.5 mg atropine sulfate on the pulmonary function of asthmatics. Hyde et al. (Ref. 8) investigated the effects in intranasal administration of atropine on saliva production. Only Jackson et al. (Ref. 9) studied the drug in the target population (allergic rhinitis); however, atropine sulfate was not studied as a single ingredient, but was part of a six-ingredient combination product containing chlorpheniramine maleate, phenylpropanolamine hydrochloride, phenylephrine hydrochloride, and three anticholinergics (hyoscyamine sulfate, atropine sulfate, and scopolamine hydrobromide).

The agency concludes that there are insufficient data at this time to support general recognition of the safety and effectiveness of the OTC use of atropine sulfate as an anticholinergic. Therefore, atropine sulfate is not included as a monograph condition in this final rule. It will be necessary for manufacturers to reformulate any OTC cough-cold drug products containing this ingredient unless the product has an approved NDA.

The agency acknowledges that many products used to treat colds contain ingredients, such as antihistamines, that can cause drowsiness and thus create a problem for persons in the work environment. However, the comment's contention that atropine sulfate does not cause drowsiness and thus will increase the efficiency of the work force is irrelevant because atropine sulfate has not been demonstrated to be effective for its intended use as an anticholinergic in OTC cough-cold drug products.

In the **Federal Register** of February 8, 1983 (48 FR 5806), the agency published a notice announcing the availability of an assessment of the economic impacts of the OTC drug review. In that assessment, the agency concluded that the OTC drug review was not a major rule as defined in Executive Order 12291, but recognized that significantly large impacts might be experienced by some small firms in some years. FDA has a statutory mandate to assure that OTC drug products are safe and effective for their intended use and are properly labeled. The statute does not allow FDA to waive these important public health considerations merely because additional costs may be incurred by a manufacturer in order to achieve compliance with a monograph.

References

(1) Comment No. RPT002, Docket No. 76N-052C, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to L. Gilson, Otis Clapp & Son, Inc., coded ANS003, Docket No. 76N-052C, Dockets Management Branch.

(3) Cullumbine, H., et al., "The Effects of Atropine Sulphate Upon Healthy Male Subjects," *Quarterly Journal of Experimental Physiology*, 40:309–319, 1955.

(4) Murrin, K.R., "A Study of Oral Atropine in Healthy Adult Subjects," *British Journal of Anaesthesia*, 45:475–480, 1973.

(5) Mirakhur, R.K., "Comparative Study of the Effects of Oral and I.M. Atropine and Hyoscine in Volunteers," *British Journal of Anaesthesia*, 50:591–598, 1978.

(6) Joseph, M.C., et al., "Premedication With Atropine by Mouth," *Lancet*, 2:1060–1061, 1960.

(7) Light, R.W., et. al., "Oral Atropine in the Treatment of Chronic Asthma," *Annals of Allergy*, 38:58–61, 1977.

(8) Hyde, R.W., et al., "Absorption from the Nasal Mucous Membrane," *Annals of Otology, Rhinology, and Laryngology*, 62:957–968, 1953.

(9) Jackson, R.H., et al., "Ru-Tuss in the Symptomatic Treatment of Allergic Rhinitis," *Annals of Allergy*, 35:172–174, 1975.

C. Comments on OTC Anticholinergic Labeling

6. One comment noted its continuing position that FDA cannot legally and should not, as a matter of policy, prescribe exclusive lists of terms from which indications for use for OTC drugs must be drawn, thereby prohibiting alternative OTC drug labeling terminology that is truthful, not misleading, and intelligible to the consumer. The comment added that these views were presented to FDA in oral and written testimony in connection with the September 29, 1982 agency hearing on the exclusivity policy.

The comment added that these labeling restrictions prevent the use of words that have been widely understood and commonly used for generations on OTC medications. The comment stated that the industry has long encouraged an agency policy that would allow choice in labeling nonprescription medicines for consumer use and urged the Commissioner to avoid restricting alternative labeling not only in this monograph but also in future proposed rulemakings.

During the course of the OTC drug review, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph. (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 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 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. In a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002), FDA announced that a hearing would be held to assist the agency in resolving this issue. On September 29, 1982, FDA conducted an open public forum 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 (alertness aids) (published in the

Federal Register of June 13, 1978; 43 FR 25544).

After considering the record, in the Federal Register of April 22, 1985 (50 FR 15810), FDA proposed to change its exclusivity policy for the labeling of OTC drug products. As proposed, manufacturers may select one of the following options:

(1) The label and labeling would contain within a boxed area designated "APPROVED USES" the specific wording on indications for use established under an OTC drug monograph. The boxed area would be required to be displayed in a prominent and conspicuous location. As under the present policy, the labeling in the boxed area would be required to be stated in the exact language of the monograph. However, with this option a statement that the information in the box was published by the Food and Drug Administration would appear either in the box or reasonably close by. At the manufacturer's option, the designation of the boxed area and the statement that the labeling was established by FDA could be combined.

(2) As a complete alternative to using the boxed area designated "APPROVED USES," the proposal would for the first time allow manufacturers an option to use other truthful and nondeceptive statements relating only to the indications established in an applicable monograph subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling. If this alternative is selected, the manufacturer would not be able to use a boxed area or include a statement that the indications are endorsed by the Food and Drug Administration.

(3) As a third alternative, manufacturers could use both a boxed area with the monograph language and also, elsewhere in the labeling, use other non-monograph language that meets the statutory standards of truthfulness and accuracy.

Regardless, other aspects of OTC drug labeling, such as the statement of identity, warnings, and directions, would continue to be required to comply with the monograph, including following any exact language established in the monograph.

The proposal to change the exclusivity policy provides for 90 days of public comment. After considering all comments submitted, the agency will announce its final decision on this matter, in a future issue of the Federal Register.

7. One comment objected to the agency's limiting the statement of identity of anticholinergic drug products to only one term, i.e., "anticholinergic." The comment urged FDA to allow manufacturers alternative ways of expressing the statement of identity in accord with 21 CFR 201.61, which allows the statement of identity to include an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. The comment stated that by using the principal intended actions to describe these products instead of using only their pharmacologic categories, an anticholinergic could be described as a product "for the relief of running nose." The comment added that such a description would have more meaning to laymen and should not be prohibited.

Wherever possible, the agency prefers to use the general pharmacologic category as the statement of identity because information on the principal intended action of the product is provided in the indications section. However, in instances where the pharmacologic category is not appropriate as the statement of identity, the principal intended action is used. For example, the statement of identity for an antihistamine used as a nighttime sleep-aid is "nighttime sleep-aid."

The alternative statement of identity suggested by the comment for anticholinergic drug products is similar to the indications statement that was proposed for these drugs in § 341.70(b) of the tentative final monograph (47 FR 30009). Because there are no anticholinergic ingredients included in this final rule, no statement of identity for anticholinergics is included in this document.

8. Referring to the proposed warning for anticholinergic drugs in § 341.70(c)(3), "Do not take this product if you have asthma, glaucoma, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." one comment stated that there is insufficient evidence to suggest that anticholinergics are harmful in asthma and noted that inhaled anticholinergic agents can be very valuable anti-asthmatic drugs. The comment also stated that the warning presumably should apply to any obstructive pulmonary disease in which clearance of secretions is a major problem, and that while some asthmatics may have this problem, not all asthmatics do.

The agency recognizes that anticholinergic drugs such as atropine have been administered by inhalation to induce bronchial dilatation when treating asthma; however, these drugs are not commonly used by physicians because of their undesirable drying side effects (Refs. 1 and 2). Ipratropium bromide, a new anticholinergic drug for inhalation use, it currently being studied and may be preferable to atropine; however, at this time, ipratropium bromide is available only for experimental use in the United States by qualified scientific investigators (Refs. 1, 3, and 4). Anticholinergics, such as atropine, can be helpful in asthma when given by inhalation; however, when given orally, atropine can reduce the volume of bronchial secretions and cause thickening of the secretions, which may lead to dangerous obstruction and infection of the respiratory airways (Ref. 1). Although all asthmatics may not have the same symptoms or problems with clearance of viscous secretions, the agency believes that, in general, the OTC use of anticholinergics by asthmatics should be discouraged in the interest of safety and a warning against use of anticholinergics by asthmatics would be necessary if an anticholinergic achieves monograph status.

The agency agrees with the comment's statement that a warning against use of anticholinergics should also apply to any obstructive pulmonary disease in which clearance of secretions is a problem. The Panel also stated that it is important to avoid anticholinergics in the presence of bronchial asthma or chronic obstructive pulmonary disease because of the possibility that anticholinergics may cause secretions to become less fluid and difficult to remove, and thus cause obstruction of the respiratory passages (41 FR 38377). The Panel's recommended warning in § 341.70(b)(3) included asthma, but did not include chronic obstructive pulmonary disease as a contraindication for the use of anticholinergics; however, the agency believes that it would be appropriate to expand the warning to include all types of chronic obstructive pulmonary disease. This term applies to patients with clinically significant, irreversible, generalized airways obstruction associated with varying degrees of chronic bronchitis, abnormalities in small airways, and/or emphysema (Ref. 5).

At this time, there are no anticholinergic ingredients that are safe and effective for inclusion in an OTC monograph; thus, no labeling for anticholinergic drugs is being proposed. However, in the event that any anticholinergic ingredient reaches monograph status, the agency will determine appropriate labeling at that time.

References

(1) Weiner, N., "Atropine, Scopolamine, and Related Antimuscarinic Drugs," *in* "The Pharmacological Basis of Therapeutics," 6th Ed., edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., Inc., New York, pp. 134–135, 1980.

(2) Weiss, E.B., and M.S. Segal, editors, "Bronchial Asthma Mechanisms and Therapeutics," Little, Brown, and Company, Boston, p. 325, 1976.

(3) Groggins, R.C., A.D. Milner, and G.M. Stokes, "Bronchodilator Effects of Clemastine, Ipratropium Bromide, and Salbutamol in Preschool Children with Asthma," *Archives of Diseases in Childhood*, 56:342–344, 1981.

(4) Poppius, H., and Y. Salorinne, "Comparative Trial of a New Anticholinergic Bronchodilator Sch 1000, and Salbutamol in Chronic Bronchitis," *British Medical Journal*, 4:134–136, 1973.

(5) Berkow, R., editor, "The Merck Manual," 14th Ed., Merck Sharp & Dohme Research Laboratories, Rahway, NJ, pp. 628–635, 1982.

9. Three comments disagreed with the agency's proposed substitution of the word "doctor" for "physician" in OTC drug labeling. One 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 the change, which would be costly and provide no benefit. 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 other two comments added that the term "physician" is clearly defined as a person licensed to practice medicine, whereas the term "doctor" is ambiguous and much more general. One of these comments recommended that FDA not eliminate "physician," the more specific term, but allow flexibility to use either term.

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 consumers and that the word "doctor" is likely to be more commonly used and better understood by consumers. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor."

10. One comment objected to elimination of the term "Caution(s)" in the labeling of OTC drug products. The comment claimed that a warning precludes use under certain conditions, whereas "caution" does not preclude use, but may often alert the consumer to a potential problem, e.g., "Caution: If irritation develops discontinue use and consult a physician." Thus, the word "warning" is harsher than "caution." The comment stated that a caution may also be used to add emphasis, e.g., "Caution: Use only as directed," or to alert the user to a special need regarding the care of a product, e.g., "Caution: Keep out of direct sunlight;" "Store in refrigerator;" "Replace bottle cap."

The comment argued that it would undoubtedly dilute the impact of essential warning statements if "cautions," which require the consumer to take certain precautions while using the product, were intermingled with "warnings," which signal that the product should not be used at all under specified circumstances. The comment asserted that although both types of statements are usually used to call attention to danger, the distinction is important, particularly when products contain long lists of warnings. The comment added that because the same phrases may be warnings with regard to one class of products and merely cautions with regard to another, the flexibility of both terms is essential in order to prepare accurate and comprehensible labeling.

Section 502(f)(2) of the act (21 U.S.C. 352(f)(2)) states, in part, that any drug marketed OTC must bear in labeling ". . . such adequate warnings . . . as are necessary for the protection of users . . . ." Section 330.10(a)(4)(v) of the OTC drug regulations provides that labeling of OTC drug products should include ". . . warnings against unsafe use, side effects, and adverse reactions . . . ."

The agency notes that historically there has not been consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. The agency considers the word "warning" alone to be the simplest, clearest signal to consumers. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems. However, as stated earlier, because there are no anticholinergic ingredients included in this final rule, no labeling for anticholinergics is included in this document.

II. Summary of Significant Changes From the Proposed Rule

Because no anticholinergic active ingredients are generally recognized as safe and effective and not misbranded, §§ 341.3 and 341.70, which contain the proposed definition and labeling of anticholinergic drugs, respectively, are not included in this final rule. (See comments 3 and 7 above.) Rather, the agency is amending Part 310 to include anticholinergic ingredients by adding to Subpart E new § 310.533 (21 CFR 310.533).

III. The Agency's Final Conclusions on OTC Anticholinergic Drug Products

The agency has determined that no anticholinergic active ingredient has been found to be generally recognized as safe and effective and not misbranded for use in OTC cough-cold drug products. Therefore, all anticholinergic ingredients, including atropine sulfate, belladonna alkaloids containing atropine (*d*-, *dl*-hyoscyamine) and scopolamine (*l*-hyoscine), and belladonna alkaloids (as contained in Atropa belladonna and Datura stramonium), which were reviewed by the Panel, are considered nonmonograph ingredients and misbranded under section 502(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(a)) and must be removed from OTC cough-cold drug products by the effective date of this final rule unless the product has an approved NDA.

In response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 30009), one comment was received. (See comment 5 above.) 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 anticholinergic 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 anticholinergic 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 310

New drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended in Part 310 as follows:

1. The authority citation for Part 310 continues to read as follows:

Authority: Secs. 502, 503, 505, 710, 52 stat. 1051, 1052, 1053, 1055 as amended (21 U.S.C. 352, 353, 355, 371); 5 U.S.C. 553; 21 CFR 5.11.

2. In Subpart E by adding new § 310.533 to read as follows:

PART 310—NEW DRUGS

§ 310.533 Drug products containing active ingredients offered over-the-counter (OTC) for human use as an anticholinergic in cough-cold drug products.

(a) Atropine sulfate, belladonna alkaloids, and belladonna alkaloids as contained in Atropa belladonna and Datura stramonium have been present as ingredients in cough-cold drug products for use as an anticholinergic. Anticholinergic drugs have been marketed OTC in cough-cold drug products to relieve excessive secretions of the nose and eyes, symptoms that are commonly associated with hay fever, allergy, rhinitis, and the common cold. Atropine sulfate for oral use as an anticholinergic is probably safe at dosages that have been used in marketed cough-cold products (0.2 to 0.3 milligram); however, there are inadequate data to establish general recognition of the effectiveness of this ingredient. The belladonna alkaloids, which contain atropine (*d, dl* hyoscyamine) and scopolamine (*l*-hyoscine), are probably safe for oral use at dosages that have been used in marketed cough-cold products (0.2 milligram) but there are inadequate data to establish general recognition of the effectiveness of these ingredients as an anticholinergic for cough-cold use. Belladonna alkaloids for inhalation use, as contained in Atropa belladonna and Datura stramonium, are neither safe nor effective as an OTC anticholinergic. There are inadequate safety and effectiveness data to establish general recognition of the safety and/or effectiveness or any of these ingredients, or any other ingredient, for OTC use as an anticholinergic in cough-cold drug products.

(b) Any OTC cough-cold drug product that is labeled, represented, or promoted for use as an anticholinergic is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FDA–1571) (OMB Approval No. 0910–0014), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any cough-cold drug product labeled, represented, or promoted OTC as an anticholinergic is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any such OTC cough-cold drug product that is labeled, represented, or promoted for use as an anticholinergic may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application.

Frank E. Young,

Commissioner of Food and Drugs.

Dated: October 7, 1985.

Margaret M. Heckler,

Secretary of Health and Human Services.

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