

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 341**

[Docket No. 76N-052H]

RIN 0910-AA01

**Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Reopening of the Administrative Record for Antihistamine Drug Products**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Reopening of the administrative record.

**SUMMARY:** The Food and Drug Administration (FDA) is reopening the administrative record for over-the-counter (OTC) antihistamine drug products to accept comments on recommendations concerning the use of these products to relieve symptoms of sneezing and runny nose associated with the common cold made at a joint advisory committee meeting on November 16, 1995. The agency is inviting comments on its tentative position that there is sufficient basis to include the use of OTC antihistamines for these symptoms in the final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. This reopening is part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Submit written comments by November 24, 2000.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Cazemiro R. Martin, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In the *Federal Register* of September 9, 1976 (41 FR 38312), FDA published, under 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 (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. The Panel recommended that antihistamines be Category III (available data are insufficient to classify as safe and effective, and further testing is required) for treating symptoms associated with the common cold (41 FR 38312 at 38380 and 38381).

In response to the Panel's Category III recommendation, two manufacturers submitted data to support the use of chlorpheniramine maleate for the relief of cold symptoms. Based on these data, the agency proposed an indication for the temporary relief of runny nose and sneezing associated with the common cold in § 341.72(b) (21 CFR 341.72(b)) of the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2203, 2204, 2216, and 2217, January 15, 1985). The agency stated in the tentative final monograph that the pharmacologic actions of the various Category I antihistamines are similar; thus, the indications stated in § 341.72 were proposed for all antihistamines included in 21 CFR 341.12 of the tentative final monograph. An amendment to the tentative final monograph was published in 1987 that included doxylamine succinate and chlorcyclizine hydrochloride as Category I ingredients for the same claims as all Category I antihistamine ingredients (52 FR 31892, August 24, 1987).

Subsequent to the tentative final monograph, the agency evaluated supplemental new drug applications requesting a prescription-to-OTC switch for drug products containing a nonmonograph antihistamine. Some applications requested labeling for treating symptoms associated with the common cold based on similarity of pharmacologic action to the antihistamines included in the tentative final monograph without direct support from clinical studies. In considering these applications, the agency questioned whether the pharmacologic effects of these newer antihistamines are sufficiently similar to the pharmacologic actions of older, monograph antihistamines.

At that time, the agency was aware that the scientific community was divided over the effectiveness of antihistamine ingredients for symptoms of the common cold. In the final rule for OTC antihistamine drug products (57 FR 58356, December 9, 1992), the agency deferred its final action on labeling for common cold symptoms for OTC antihistamines in order to evaluate

data that had become available after publication of the tentative final monograph. The agency stated its intention to further evaluate whether data on chlorpheniramine maleate to relieve sneezing and runny nose associated with the common cold could be extrapolated to other antihistamines included in the final monograph or to other antihistamines that may be switched from prescription to OTC status. The agency further stated its intention to evaluate more recent clinical studies as well as the older data concerning the effectiveness of antihistamines in treating symptoms of the common cold. The agency solicited all studies, negative as well as positive, from drug manufacturers and the Consumer Healthcare Products Association (formerly the Nonprescription Drug Manufacturers Association), and searched its own files and the published literature. In 1992, the agency formed a task force that consisted of agency staff, FDA Staff Fellows, and outside consultants, to assess the available data on OTC antihistamines that would help resolve these issues.

In order to be included in the agency's evaluation, a study had to meet certain inclusion criteria developed by the task force, as follows: (1) The study must be double-blind, randomized, and placebo controlled; (2) the antihistamine in the common cold medication must be a single ingredient; (3) the common cold had to exist for no more than 2 days before the first application of study medication; (4) subjects needed to have runny nose of at least moderate intensity at baseline before any medication; and (5) the severity of the runny nose had to be evaluated at baseline and at least once after administration of medication during both the first and second days of medication (Ref. 1).

The task force evaluated all of the submitted studies and determined that nine generally met these requirements (three using chlorpheniramine maleate and six using doxylamine succinate). The task force then did a meta-analysis on these studies, comparing the active ingredients to placebo for both increment scores (change from baseline) and goal of therapy (50 percent reduction or complete cessation of symptom). The symptoms evaluated by the task force were runny nose and sneezing on each of 2-study days. Using these parameters and analyses, the task force found that the antihistamines studied had an effect on runny nose and sneezing in the early phases of the common cold (Ref. 2).

The task force presented the results of its meta-analysis to a joint meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee (the Committees) held on November 15, 1994 (Ref. 2). The Committees were not asked for a recommendation at that time. The following year, on November 16, 1995, the Committees met again and discussed the analysis (Ref. 3). At this meeting, the Committees concluded that the meta-analysis supports the use of chlorpheniramine maleate and doxylamine succinate to relieve the symptoms of runny nose and sneezing associated with the common cold. However, the Committees voted against extrapolating the data on these two ingredients to all Category I antihistamines because they had insufficient data regarding the active mechanism of these drugs in relief of symptoms of the common cold. Some members raised the issue of comparative potency relative to anticholinergic and/or antihistaminic effects of other Category I antihistamines.

## II. The Agency's Discussion of the Committees' Recommendations

The agency believes that sufficient basis currently exists for all Category I antihistamine ingredients to have the indication of relief of sneezing and runny nose due to the common cold. Studies published after the task force's meta-analysis suggest that other antihistamines, brompheniramine maleate (Ref. 4) and clemastine fumarate (Ref. 5), are effective for relief of sneezing and runny nose associated with the common cold. Both studies reported therapeutic effects against cold symptoms similar to those seen against allergic rhinitis symptoms, which is their currently approved indication. Data from the brompheniramine study were submitted to the agency (Ref. 6). However, because the administrative record is currently closed, the study and supporting documentation will not be discussed here but will be discussed in the final rule along with any new information that comes to the agency's attention.

Ingredients in this class have pharmacologic actions and therapeutic applications in common and are generally discussed together (Ref. 7). These ingredients are known to be effective H<sub>1</sub> antagonists, and some studies have demonstrated the release of histamine following rhinovirus challenge in allergic individuals (Refs. 8 and 9). Further, the monograph antihistamines exert mild to moderate anticholinergic effects and are effective in drying nasal secretions (Refs. 2 and

10 through 15). Therefore, the agency believes that populations of consumers exist who would benefit from either of these effects (antihistaminic or anticholinergic) on cold symptoms.

Additionally, the agency believes that some of the controversy over the use of antihistamines for the common cold may have originated from their early promotion as "cures" or "preventatives" (Ref. 16). It is now known that Category I antihistamine ingredients do not cure or prevent the common cold, but rather are palliative agents that are useful for reducing nasal discharge (runny nose) and sneezing (Refs. 4, 5, 12, and 17). Suppression of sneezing and other cold symptoms may help reduce the spread of the cold virus and thus have a public health impact (Ref. 4). The literature and the meta-analysis of data conducted by the agency's task force support these uses for OTC common cold symptom relief.

The agency believes that OTC antihistamine ingredients effectively relieve cold symptoms in populations of consumers and should remain available for that use. Unless the agency receives convincing data to refute its tentative position, it intends to publish a final monograph for OTC antihistamine drug products that includes the indication for relief of sneezing and runny nose associated with the common cold proposed in § 341.72(b)(2) (50 FR 2200 at 2216). Therefore, the agency is reopening the administrative record for the rulemaking for OTC antihistamine drug products to accept comments concerning the use of these products to relieve symptoms of sneezing and runny nose associated with the common cold.

## III. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. D'Agostino, R. B., and M. Weintraub, "Meta-Analysis: A Method for Synthesizing Research," *Clinical Pharmacology and Therapeutics*, vol. 58, pp. 605-616, 1995.
2. Transcript of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Drugs Advisory Committee, November 15, 1994, pp. 11-113, in OTC vol. 04HFMA2, Docket No. 76N-052H, Dockets Management Branch.
3. Transcript of the Joint Meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committees, November 16, 1995, pp. 191-333, in OTC vol. 04HFMA2, Docket No. 76N-052H, Dockets Management Branch.
4. Gwaltney, J. M., and H. M. Druce, "Efficacy of Brompheniramine Maleate for the Treatment of Rhinovirus Colds," *Clinical*

*Infectious Diseases*, vol. 25, pp. 1188-1194, 1997.

5. Turner, R. B. et al., "Effectiveness of Clemastine Fumarate for Treatment of Rhinorrhea and Sneezing Associated with the Common Cold," *Clinical Infectious Diseases*, vol. 25, pp. 824-830, 1997.

6. Comment No. C229, Docket No. 76N-052H, Dockets Management Branch.

7. Douglas, W. W., "Antihistamines," in *The Pharmacological Basis of Therapeutics*, 4th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 635-645, 1970.

8. Thomas, L. H. et al., "Leukocyte Responses to Experimental Infection with Human Rhinovirus," *The Journal of Allergy and Clinical Immunology*, vol. 94, pp. 1255-1262, 1994.

9. Calhoun, W. J. et al., "A Common Cold Virus, Rhinovirus 16, Potentiates Airway Inflammation after Segmental Antigen Bronchoprovocation in Allergic Subjects," *The Journal of Clinical Investigation*, vol. 94, pp. 2200-2208, 1994.

10. Pearlman, D. S., "Antihistamines: Pharmacology and Clinical Use," *Drugs*, vol. 12, pp. 258-273, 1976.

11. Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, vol. 27, pp. 542-573, 1947.

12. Cooper, J. W., "H-1 Blockers—Classical Antihistamines," *New England and Regional Allergy Proceedings*, vol. 7, pp. 356-361, 1986.

13. Darling, C. M., "Chapter 16—Histamine and Antihistaminic Agents," in *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 8th Ed., edited by R. F. Doerge, J. B. Lippincott Co., Philadelphia, pp. 583-606, 1982.

14. The United States Pharmacopeial Convention, Inc., "Antihistamines-Systemic," in *USP DI, Drug Information for the Health Care Professional*, Rand McNally, Taunton, MA, pp. 302-309, 1995.

15. Berkow, R., editor, *The Merck Manual*, 14th Ed., Merck & Co., Inc., Rahway, NJ, pp. 2397-2403, 1982.

16. Feller, A. E. et al., "The Failure of Antihistaminic Drugs to Prevent or Cure the Common Cold and Undifferentiated Respiratory Diseases," *The New England Journal of Medicine*, vol. 242, pp. 737-744, 1950.

17. Roth, F. E., and I. I. A. Tabachnick, "Chapter 48—Histamine and Antihistamines," in *Drill's Pharmacology in Medicine*, 4th Ed., edited by J. R. DiPalma, McGraw-Hill Book Co., New York, pp. 995-1020, 1971.

## IV. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written comments by November 24, 2000. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments should be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received

comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: August 15, 2000.

**Margaret M. Dotzel,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Part 514

[Docket No. 00N-1399]

#### Presubmission Conferences

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend its new animal drug regulations to describe the procedures to be followed for requesting, conducting, and documenting presubmission conferences. Under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Animal Drug Availability Act of 1996 (ADAA), any person intending to file a new animal drug application (NADA) or supplemental (NADA) or to investigate a new animal drug is entitled to one or more conferences with FDA to reach an agreement establishing a submission or investigational requirement. This proposed regulation describes how a person would request a presubmission conference and describes the procedures for the conduct of the presubmission conference.

**DATES:** Submit written comments on the proposed rule by November 8, 2000. Submit written comments on the information collection provisions by September 25, 2000.

**ADDRESSES:** Submit written comments on the proposed rule to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

**FOR FURTHER INFORMATION CONTACT:** Gail L. Schmerfeld, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1620.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

The ADAA (Public Law 104-250) was enacted on October 9, 1996. Section 512(b)(3) of the act (21 U.S.C. 360b(b)(3)), as amended by section 2(d) of the ADAA, provides that any person intending to file an NADA or supplemental NADA or to investigate a new animal drug is entitled to one or more conferences with FDA prior to such submission or during the investigation of a new animal drug. The purpose of such a conference is to reach an agreement establishing a submission or investigational requirement. A decision establishing a submission or investigational requirement can be changed only if: (1) FDA and the potential applicant mutually agree to modify the requirement, or (2) FDA by written order determines that a substantiated scientific requirement essential to the determination of safety or effectiveness of the animal drug involved has appeared after the conference. If FDA determines that more than one field study is required to establish by substantial evidence that an intended use of a new animal drug is effective, FDA will provide written scientific justification for that decision within 25 calendar days of the conference. While section 512(b)(3) of the act does not entitle persons who intend to file an abbreviated new animal drug application (ANADA) to request a presubmission conference, such potential applicants are entitled to request presubmission conferences under this proposed rule.

Although the ADAA added a statutory entitlement to a presubmission conference, FDA's Center for Veterinary Medicine (CVM) had already been encouraging sponsors of NADA's to participate in conferences with FDA to discuss in detail what studies are necessary to demonstrate the safety and effectiveness of a new animal drug. In its experience with these presubmission conferences, FDA found that, as a result of this direct and detailed communication during the development and review of new animal drugs, fewer unusable studies were conducted and there were fewer delays in the review process. Consequently, companies saved resources and the marketing of new animal drugs became more expeditious. FDA's success with the use of presubmission conferences to establish submission requirements for new animal drugs was also reflected in its commitment to implement broad use of presubmission conferences as part of the President's reinventing government initiatives (e.g., "Reinventing the

Regulation of Animal Drugs," May 1996). The ADAA codifies FDA's use of presubmission conferences.

##### II. Description of Proposed Rule

The regulations being proposed by FDA would establish the procedures for requesting, conducting, and documenting presubmission conferences. Presubmission conferences will continue to be like those that were held between applicants and FDA prior to the enactment of the ADAA. The purpose of presubmission conferences is to allow FDA and a potential applicant, i.e., a person intending to investigate a new animal drug or to file an NADA, supplemental NADA, or ANADA, to discuss and reach agreement regarding a submission or investigational requirement. A submission or investigational requirement includes, among other things, identification of the number and types of studies that are necessary to demonstrate the safety and effectiveness of a new animal drug for the intended uses and conditions of use prescribed, recommended, or suggested in the proposed labeling for the new animal drug. Presubmission conferences give FDA and a potential applicant a means to identify the least burdensome appropriate requirements that have a reasonable likelihood of resulting in approval.

Meetings other than presubmission conferences may be necessary during the development and review of new animal drugs. Meetings in which the focus is other than to establish the safety and effectiveness data requirements for new animal drugs (e.g., meetings relating to administrative processes, protocol development, or label development) are not specifically covered by this proposed rule.

##### A. Definitions (Proposed § 514.3)

Proposed § 514.3 defines the terms "potential applicant," "presubmission conference," and "presubmission conference agreement" as those terms are used in 21 CFR part 514. "Potential applicant" means any person intending to investigate a new animal drug, file an NADA or supplement, or file an ANADA. One or more "presubmission conferences" may be needed to establish agreement regarding part or all of a submission or investigational requirement. Agreement on a submission or investigational requirement reached by a potential applicant and FDA in a presubmission conference(s) will be recorded in the "presubmission conference agreement" section of the memorandum of conference prepared by FDA and will be