

Marketing of OTC Bronchodilator Drugs

There are two regulatory mechanisms in the United States under which over-the-counter (OTC) drugs may be marketed, the new drug application (NDA) and the OTC drug monograph. New drug applications are specific for a single drug product and OTC monographs are specific to an ingredient (allowing different manufacturers to market products containing the same ingredients). Over-the-counter bronchodilators are marketed under both regulatory mechanisms. The following table highlights the bronchodilator products or ingredients eligible for marketing OTC.

Over-the Counter Bronchodilators

New Drug Applications	OTC monograph
Metered Dose Inhalers of Epinephrine <ul style="list-style-type: none"> • Wyeth • Armstrong 	Oral Dose <ul style="list-style-type: none"> • Ephedrine • Ephedrine hydrochloride • Ephedrine sulfate • Racephedrine hydrochloride Hand-held rubber bulb nebulizer <ul style="list-style-type: none"> • Epinephrine • Epinephrine bitartrate • Racepinephrine hydrochloride

The regulatory requirements for drugs marketed OTC under new drug applications are based on the same regulations that pertain to prescription drugs (e.g., reporting adverse events, manufacturing). The process for developing monographs, however, is specific to OTC drugs and different from the regulatory process that applies to prescription drugs.

The following information provides a brief overview of the OTC Drug Review process that is used to develop monographs. After this summary, there is a table that outlines the regulatory history of the development of the bronchodilator monograph. This information will be briefly summarized at the advisory committee meeting.

The OTC Drug Review to Develop OTC Monographs

In 1972, the FDA initiated a scientific review of the active ingredients that were in marketed OTC drug products, to ensure their safety and effectiveness. There were a large number of OTC pharmaceuticals already on the market at that time, so FDA decided that a product-by-product determination would not be feasible. FDA determined that it would be more efficient to focus its review on the ingredients used in each OTC therapeutic category. Newer (post-1972) OTC ingredients are generally reviewed under NDAs, which evaluate specific drug products (e.g., dosage form, inactive ingredients).

The OTC drug review is a three-phase rulemaking process. Each phase requires publication in the Federal Register and allows for a comment response from the public. The process culminates in the promulgation of regulations, establishing standards for both the active ingredients and labeling in each OTC therapeutic drug category. The three phases are as follows:

1. Advisory Panel Review and Advance Notice of Public Rulemaking (ANPR)
2. Tentative Final Monograph (TFM)
3. Final Monograph (FM)

The first phase of the OTC review was accomplished by FDA-appointed advisory review panels. Panel members included scientifically qualified individuals and non-voting, technical liaison members representing consumer and industry interests. These panels were charged with reviewing the ingredients and labeling of marketed OTC drug products to determine whether each could be classified as generally recognized as safe and effective (GRASE) for use in self-treatment.

The panels classified ingredients of OTC drug products into three categories:

- Category I: generally recognized as safe and effective (GRASE) for the claimed therapeutic indication.
- Category II: not generally recognized as safe and effective (NRASE) or having unacceptable indications.
- Category III: insufficient data available to permit final classification

The panels also recommended labeling (including therapeutic indications), dosage instructions, and warnings about side effects and potential misuse and abuse. The panels submitted a total of 59 reports to the FDA covering the various therapeutic categories. These reports and panel-recommended monographs were published in the Federal Register as advance notices of proposed rule making (ANPR). Each publication invited public comment.

The second phase of the OTC drug review is the FDA's evaluation of the panels' findings, consideration of public comment, and evaluation of any new data that may have become available. The agency then publishes its tentative conclusions as a proposed rule (tentative final monograph – TFM). This document establishes for public comment the FDA's initial position on the related scientific issues. After the TFM is published, a period of time is allotted for submission of supporting statements, objections, requests for a public hearing, and new data.

After considering objections and new data, and after processing requests for a hearing, the agency issues a final rule (i.e., the third phase), usually in the form of a final monograph (FM). Each FM is included in the Code of Federal Regulations (CFR). Usually, monographs become effective one year after publication in the FR, requiring that all affected OTC drug products meet the regulatory specifications within that time. Other final regulations, sometimes referred to as non-monographs, are developed when the existing data are insufficient to establish a monograph category or to support certain ingredients within a category. These regulations define ingredients that cannot lawfully be marketed, or claims that are unacceptable in labeling.

Under the monograph process, pre-clearance by the FDA (i.e., submission of an NDA for an OTC drug product) is not required to allow marketing of a drug product, if the regulatory standards described in the monographs have been met. The monograph

describes allowed active ingredients and labeling. Monograph regulations also specify the parameters that manufacturers must abide when formulating products.

When conditions arise that are not specified in the final OTC drug monograph regulations (i.e., new ingredients, combinations of ingredients, indications, or labeling), manufacturers may gain marketing clearance either by submitting supportive data in the form of a petition to amend a FM to include the new marketing conditions, or by submitting an NDA to cover the new conditions.

The attached table provides a brief summary of the regulatory history for the bronchodilator active ingredients included in the monograph.

Regulatory History of OTC Bronchodilator Monograph			
Date	Federal Register (FR) Citation	Action	Result
9/9/1976	41 FR 38312	Advance Notice of Proposed Rule (ANPR)	The following ingredients are included in the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) Panel's recommended monograph: 1. Ephedrine Preparations: ephedrine, ephedrine HCl, ephedrine SO ₄ , racephedrine HCl 2. Epinephrine Preparations: epinephrine, epinephrine bitartrate, epinephrine HCl (racemic) inhalant 3. Methoxyphenamine HCl 4. Theophylline Preparations: Aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate.
12/10/1976	41 FR 54032	Commissioner disagreed with Category I Status for theophylline	
10/26/1982	47 FR 47520	Proposed Rule	All Advanced Notice of Proposed Rule ingredients, except for theophylline are in the Tentative Final Monograph (TFM); metaproterenol was added to the TFM
8/30/1983	48 FR 39242	Reopening of Administrative Record to consider safety of metaproterenol	
10/2/1986	51 FR 35326	Final Rule	All TFM ingredients except for metaproterenol were included in the Final Monograph (FM). Epinephrine HCl (racemic) is named racepinephrine HCl. Oral dose: ephedrine, ephedrine sulfate or racephedrine hydrochloride. Pressurized metered-dose aerosol container or hand-held rubber bulb nebulizer: epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride
8/12/1988	53 FR 30522	Proposed Rule (Combinations)	Included a combination of either any single ephedrine ingredient with a single expectorant ingredient.
10/20/1993	58 FR 54238	Final Rule: Final Monograph A	MAOI warning added as a drug interaction precaution.
3/9/1995	60 FR 10286	Propose to amend the final monograph	Removed pressurized metered-dose aerosol container dosage forms for epinephrine epinephrine bitartrate and racepinephrine HCl because marketing will require NDA, and stated that those ingredients could be marketed in a hand-held rubber nebulizer.
7/27/1995	60 FR 38643	Propose to amend the final monograph	Removed ephedrine, ephedrine HCl, ephedrine SO ₄ and racepinephrine HCl from the monograph.
5/20/1996	61 FR 25142	Amendment to the final rule dated 10/2/1986	Finalized 3/9/95 Proposed Rule Amendment
9/27/2001	66 FR 49276	Combination FR	Declared that ephedrine or any of its salts in combination with any analgesic(s) or analgesic-antipyretic(s) anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient is a new drug.
7/13/2005	70 FR 40232	PR Amendment of combination TFM	Declared that ephedrine or any of its salts in combination with any expectorant or in combination with any oral nasal decongestant is a new drug. FDA has received comments on this PR and these are under review.
7/13/2005	70 FR 40237	PR Amendment	Added warnings to the final monograph and revised indications, warnings and directions in labeling of products containing ephedrine and its salts. Withdrew the 9/27/01 proposed rule. FDA has received comments on this PR and these are under review.