Agency, M/ADD, 301 Fourth Street SW., Washington, DC 20547, telephone (202) 619–5503; and OMB review: Mr. Jefferson Hill, Office of Information And Regulatory Affairs, Office of Management and Budget, New Executive Office Building, Washington, DC 20503, telephone (202) 395–7340.

SUPPLEMENTARY INFORMATION: Public reporting burden for this collection of information (Paper Work Reduction Project: OMB No. to be assigned) is estimated to average 15 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to the United States Information Agency, M/ADD, 301 Fourth Street SW., Washington, DC 20547; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, New Executive Office Building, Washington, DC 20503.

Title: USIA Responsible Officer Training Survey.

Form Number: IAP–136.

Abstract: Data from this information collection will be used by USIA's Office of the General Counsel (GC) to help develop training sessions for responsible officers.

Proposed Frequency of Responses:
No. of Respondents—200
Recordkeeping Hours—.15
Total Annual Burden—50

August 17, 1994.

Rose Royal,

Federal Register Liaison.

[FR Doc. 94–20585 Filed 8–22–94; 8:45 am]

BILLING CODE 8230–01–M

OFFICE OF THE UNITED STATES TRADE REPRESENTATIVE

Resolution of Complaint of Price-Undercutting of Subsidized Cheese Imports

AGENCY: Office of the United States Trade Representative.

ACTION: Notice of Resolution of Complaint of Price-Undercutting of Subsidized Cheese Imports.

SUMMARY: The Office of the United States Trade Representative (USTR) is providing notice that the European Commission and the Government of Austria have provided the necessary assurances that the duty-paid wholesale price of imported Swiss or Emmentaler cheese produced in Austria, Denmark and Germany will not be less than the domestic wholesale market price of similar articles produced in the United States.

FOR FURTHER INFORMATION CONTACT: Elizabeth Haines, Senior Economist, Office of Agricultural Affairs (202) 395–3077, Office of the United States Trade Representative.

SUPPLEMENTARY INFORMATION: On June 27, 1994, the United States Trade Representative received a letter from the Acting Secretary of Agriculture informing him of the Acting Secretary's finding that imported subsidized quota Swiss or Emmentaler cheese produced in Austria, Denmark and Germany is undercutting the wholesale price of Swiss cheese produced and sold in the United States. During the investigation period of December 1993 through April 1994, the average duty-paid wholesale price was $1.55 per pound, $1.56 per pound, and $1.12 per pound of blocks of Swiss or Emmentaler cheese imported from Austria, Denmark, and Germany, respectively, compared to the average domestic wholesale market price of $1.76 per pound of blocks of Swiss cheese produced in the United States. During the same period, the average duty-paid wholesale price was $1.80 per pound and $1.69 per pound for cuts, slices, loaves, etc., imported from Denmark and Germany, respectively, compared to the average domestic wholesale market price of $1.85 per pound for cuts, slices, loaves, etc., of Swiss cheese produced in the United States. Also during the period of investigation, the average duty-paid wholesale price was $1.37 per pound for trims and end pieces imported from Austria compared to $1.54 from trims and end pieces produced in the United States.

On June 29, in accordance with section 702(c)(2) of the Trade Agreements Act of 1979 (the Act) (19 U.S.C. 1202 note), the Office of the United States Trade Representative notified the European Commission and the Government of Austria of the price-undercutting determination made by the Acting Secretary of Agriculture, requested that corrective action be taken, and asked for appropriate assurances concerning the commitments made in the Arrangement Between the United States and Austria Concerning Cheeses, and the Arrangement Between the United States and the European Union Concerning Cheeses.

On July 11, the Government of Austria notified the United States Trade Representative that measures have been taken to ensure that the duty-paid wholesale price of imported Swiss or Emmentaler cheese produced in Austria will not be less than the domestic wholesale market price of similar cheese produced in the United States. On July 14, the European Commission notified the United States Trade Representative that measures have been taken to ensure that the duty-paid wholesale price of imported Swiss or Emmentaler cheese produced in the European Union will not be less than the domestic wholesale market price of similar cheese produced in the United States.

In addition, the European Commission and the Government of Austria gave assurances that they will respect the price commitments in the Arrangement. Since the above notifications by the European Commission and the Government of Austria have occurred within the 15-day period provided in section 702(c)(3) of the Act, no further action is required pursuant to section 702.

Michael Kantor,

United States Trade Representative.

[FR Doc. 94–20650 Filed 8–22–94; 8:45 am]

BILLING CODE 3190–01–M

Sunshine Act Meetings

Federal Register
Vol. 59, No. 162
Tuesday, August 23, 1994

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

NUCLEAR REGULATORY COMMISSION

DATE: Weeks of August 22, 29, September 5, and 12, 1994.

PLACE: Commissioners' Conference Room, 11555 Rockville Pike, Rockville, Maryland.

STATUS: Public and Closed.

MATTERS TO BE CONSIDERED:

Week of August 22

Monday, August 22

9:00 a.m.
Discussion of Interagency Issues (Closed—Ex. 9)

9:00 a.m.
Briefing on Investigative Matters (Closed—Ex. 5 and 7)

2:00 p.m.
Briefing on Additional Changes to Part 100 Rulemaking and Proposed Update on Source Term (Public Meeting)
(Contact: Leonard Soffer, 301–415–6574)

Tuesday, August 23

9:30 a.m.
Periodic Briefing on EEO Program (Public Meeting)
(Contact: Vandy Miller, 301–415–7380)

11:30 a.m.
Affirmation/Discussion and Vote (Public Meeting)
a. Gulf States Utilities Company—Appeal of LBP–94–3 (River Bend Station Unit 1) (Tentative)
(Contact: Cecilia Carson, 301–504–1625)
b. Sequoyah Fuels Corporation's and General Atomics' Appeals of the Atomic Safety and Licensing Board's Orders, LBP–94–5 and LBP–94–8 (Docket No. 40–8027–EA) (Tentative)
(Contact: Cecilia Carson, 301–504–1625)
c. Sequoyah Fuels Corporation's Appeal of the Atomic Safety and Licensing Board's Order LBP–94–19 (Docket No. 40–8027–EA) (Tentative)
(Contact: Cecilia Carson, 301–504–1625)
d. Sequoyah Fuels Corp. General Atomics' Petition for Review and/or Motion for Directed Certification (Docket No. 40–8037–EA) (Tentative)
(Contact: Roland Frye, 301–504–3505)

Week of August 29—Tentative

Tuesday, August 30

2:30 p.m.
Briefing on PRA Policy Statement and Action Plan (Public Meeting)
Contact: Thomas Hiltz, 301–504–1105)

Wednesday, August 31

10:00 a.m.
Briefing by U.S. Enrichment Corporation (Public Meeting)

11:30 a.m.
Affirmation/Discussion and Vote (Public Meeting) (if needed)

Week of September 5—Tentative

Wednesday, September 7

2:00 p.m.
Briefing on Information Technology Strategic Plan (Public Meeting)
(Contact: Richard Hartfield, 301–415–5818)

Thursday, September 8

1:30 p.m.
Periodic Meeting with Advisory Committee on Reactor Safeguards (ACRS) (Public Meeting)
(Contact: John Larkins, 301–415–7360)

3:00 p.m.
Briefing on NRC High Level Radioactive Waste Performance Assessment Program (Public Meeting)
(Contact: Norman Eisenberg, 301–415–7285)

4:30 p.m.
Affirmation/Discussion and Vote (Public Meeting) (if needed)

Friday, September 9

9:30 a.m.
Briefing on HLW Issues by NWTRB, State of Nevada, Local Governments and Native Americans (Public Meeting)
(Contact: Chip Cameron, 301–504–1642)

1:30 p.m.
Protocol for Study of Thyroid Disease in Belarus as a Result of the Chernobyl Accident (Public Meeting)
(Contact: Shlomo Yaniv, 301–415–6239)

4Week of September 12—Tentative

There are no meetings scheduled for the Week of September 12.

ADDITIONAL INFORMATION: By a vote of 3–0 on August 19, the Commission determined pursuant to U.S.C. 552b(e) and § 9.107(a) of the Commission's rules that "Discussion of Interagency Issues" (Closed—Ex. 9) be held on August 22, and on less than one week's notice to the public.

By a vote of 3–0 on August 19, the Commission determined pursuant to U.S.C. 552b(e) and § 9.107(a) of the Commission's rules that "Briefing on Investigative Matters" (Closed—Ex. 5 and 7) be held on August 22, and on less than one week's notice to the public.

By a vote of 3–0 on August 19, the Commission determined pursuant to U.S.C. 552(e) and § 9.107(a) of the Commission's rules that "Affirmation of Sequoyah Fuels Corp. General Atomics' Petition for Review and/or Motion for Directed Certification (Docket No. 40–8027–EA)" (Public Meeting) be held on August 22, and on less than one week's notice to the public.

Note: Affirmation sessions are initially scheduled and announced to the public on a time-reserved basis. Supplementary notice is provided in accordance with the Sunshine Act as specific items are identified and added to the meeting agenda. If there is no specific subject listed for affirmation, this means that no item has as yet been identified as requiring any Commission vote on this date.

The schedule for Commission meetings is subject to change on short notice. To verify the status of meetings call (Recording)—(301) 504–1292.

CONTACT PERSON FOR MORE INFORMATION: William Hill, (301) 504–1661.

Dated: August 19, 1994.

William M. Hill, Jr.

SECY Tracking Officer, Office of the Secretary.

FR Doc. 94–20840 Filed 8–19–94; 3:09 pm]

BILLING CODE 7590–01–M

federal register

Tuesday
August 23, 1994

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 310, et al.
Final Monograph for OTC Nasal Decongestant Drug Products; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 341, and 369

[Docket No. 76N–052N]

RIN 0905–AA06

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products

AGENCY: Food and Drug Administration, HHS.

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) nasal decongestant drug products (drug products used to relieve nasal congestion caused by acute or chronic rhinitis) 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 nasal decongestant drug products that have come to the agency's attention. Also, this final rule amends the regulation that lists nonmonograph active ingredients by adding those OTC nasal decongestant ingredients that have been found to be not generally recognized as safe and effective and that were not previously listed in the regulation. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: August 23, 1995.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

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 (Cough-Cold Panel), 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 Cough-Cold Panel were put on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulations, in the form of tentative final monographs, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products were issued in the following segments: Anticholinergics and expectorants, bronchodilators, antitussives, nasal decongestants, antihistamines, and combinations. The fourth segment, the tentative final monograph for OTC nasal decongestant drug products, was published in the **Federal Register** of January 15, 1985 (50 FR 2220). Interested persons were invited to file by May 15, 1985, 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 May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986.

In the **Federal Register** of June 19, 1992 (57 FR 27658), FDA published a notice of proposed rulemaking to amend the tentative final monograph for OTC nasal decongestant drug products to modify the drug interaction precaution statement as follows:

Drug interaction precaution. Do not take this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression or psychiatric or emotional conditions), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

In the **Federal Register** of July 30, 1992 (57 FR 33663), FDA published a correction to change the wording of the first sentence of the statement from, "Do not take * * *" to "Do not use * * *." In the **Federal Register** of August 6, 1992 (57 FR 34734), the agency extended the comment period to October 5, 1992, to obtain additional comments on whether the drug interaction precaution statement should be expanded to include MAO B drugs, such as selegiline. The agency asked whether the proposed drug interaction precaution statement should be expanded to read:

Drug interaction precaution. Do not use this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

The agency invited comments and information on interactions between selegiline and sympathomimetic amines and asked whether, from a public health perspective, it would be appropriate to expand the drug interaction precaution statement, as indicated. Final agency action occurs with the publication of this final monograph, which is the final rule establishing a monograph for OTC nasal decongestant drug products (see comment 22 in section I.E. of this document.)

The Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) reviewed safety and effectiveness data on two oral nasal decongestant ingredients, phenylephrine hydrochloride and phenylpropanolamine hydrochloride (in lozenge form), and classified these nasal decongestants in Category III in its report on OTC oral health care drug products published in the **Federal Register** of May 25, 1982 (47 FR 22920). In the tentative final monograph for OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products published in the **Federal Register** of January 27, 1988 (53 FR 2448), the agency referred the data on these two oral nasal decongestant ingredients to the rulemaking for OTC nasal decongestant drug products because most of the nasal decongestant ingredients had been reviewed earlier and more extensively by the Cough-Cold Panel. In this final rule, phenylephrine hydrochloride for use as an oral nasal decongestant, which would include use in a lozenge dosage form, is a monograph ingredient. However, because of still unresolved safety issues concerning phenylpropanolamine preparations, the agency is deferring action on this drug. (See the **Federal Register** of January 15, 1985, 50 FR 2220 at 2221.) Therefore, phenylpropanolamine preparations will not be categorized or further discussed in this document.

Propylhexedrine was formerly a scheduled drug both domestically and internationally, but had an exclusion under 21 CFR 1308.22 that allowed it to

be sold OTC in the United States in inhaler products. In September 1990, the 27th World Health Organization (WHO) Expert Committee on Drug Dependence examined the international scheduling of propylhexedrine. Based on new data, the Expert Committee recommended to WHO that propylhexedrine be removed from international control. On June 10, 1991, the United States was notified that propylhexedrine had been decontrolled internationally, thus obviating the need for domestic control. The Drug Enforcement Administration issued a final rule in the **Federal Register** of December 3, 1991 (56 FR 61372) to remove propylhexedrine from the schedules of the Controlled Substances Act.

The ingredient l-desoxyephedrine is currently a scheduled drug in the United States. However, a specific marketed inhaler product containing this topical nasal decongestant ingredient has an exclusion that allows it to be sold OTC in the United States (see 21 CFR 1308.22). Thus, this ingredient for topical use in an inhaler dosage form could be included in this final monograph (See paragraph 19 in section II of this document.)

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 all OTC nasal decongestant drug products, except those containing phenylpropanolamine, occurs with the publication of this final monograph, which establishes §§ 341.3(f) and (g), 341.20, and 341.80 for OTC nasal decongestant drug products in part 341 (21 CFR part 341). Combination drug products containing nasal decongestant ingredients are addressed in the tentative final monograph on OTC combination cough-cold drug products, which was published in the **Federal Register** of August 12, 1988 (53 FR 30522). A final rule for those combination products will be published in a future issue of the **Federal Register**.

The OTC drug procedural regulations (21 CFR 330.10) 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 does not use 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. In place of Category I, the term "monograph conditions" is used; in place of Category II or III, the term "nonmonograph conditions" is used.

As discussed in the proposed rule on OTC nasal decongestant drug products (50 FR 2220), the agency advised 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 12 months after the date of publication in the **Federal Register**. Therefore, on or after August 23, 1995, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition 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 it is the subject of an approved application or abbreviated application (hereinafter called application). Further, any OTC drug product subject to this monograph that is 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 rule on OTC nasal decongestant drug products, 11 drug manufacturers, 1 drug manufacturers' association, 1 health care professional, and 11 consumers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above). 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.

In proceeding with this final monograph, the agency has considered all comments and objections, and the changes in the procedural regulations.

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 (address above).

I. The Agency's Conclusions on the Comments

A. General Comments on OTC Nasal Decongestant 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 at 9471 to 9472); in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260); and in paragraph 2 of the preamble to the tentative final monograph for OTC cough-cold combination drug products, published in the **Federal Register** of August 12, 1988 (53 FR 30522 at 30524). FDA reaffirms the conclusions stated in those documents. 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 Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. Two comments stated that nasal decongestants cause dependency and should not be available OTC. One of the comments, from a physician, observed that a relatively large number of individuals with upper respiratory symptoms (often associated with allergic rhinitis) begin taking nasal decongestants and find that the symptoms persist for longer than 1 week and often persist for several months at a time. Furthermore, if the individuals attempt to use nasal decongestants for the duration of this period, there is a high likelihood that they will develop a tolerance of the nasal mucosa to the decongestant effect of the medication. When the individuals try to stop the medication, they develop a significant obstructive congestion of the nasal mucosa from which they only apparently find relief through continued use of the medicine. Also, the medication appears to lose its effect, somewhat, with continued use over a long period of time, thus requiring even more frequent use. The comment stated this was particularly a problem with

nasal sprays and cited several patients who persisted in using OTC nasal sprays every 2 hours or so despite intensive efforts by the physician to discourage such use. The comment contended that easy accessibility of these products, due to their OTC status, makes it almost impossible to wean some patients from the use of nasal decongestants. The second comment, from a consumer, opposed OTC use of nasal decongestants because of experience in which a member of the family became dependent on nasal decongestant sprays in order to breathe.

The agency has reexamined the Cough-Cold Panel's discussion regarding "rebound congestion." The Cough-Cold Panel stated the following:

> Because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is the tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time. Continued and intense drug-induced vasoconstriction can lead to rebound dilation of the blood vessels as the drug effect subsides. This phenomenon, which intensifies nasal congestion and perpetuates the rhinitis condition, has been termed "rebound congestion." This problem is minimized if topically applied decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days. (See 41 FR 38312 at 38396.)

Although aware that continued use of nasal decongestant drugs might result in rebound congestion, the Cough-Cold Panel thought that the clinical and marketing data it reviewed showed these drugs to be safe and effective when used according to label directions. Therefore, the Cough-Cold Panel concluded that such drugs should be available for OTC use and it recommended the following warning: "Do not use this product for more than 3 days. If symptoms persist, consult a physician" (41 FR 38312 at 38423).

In the tentative final monograph, the agency concurred with the Cough-Cold Panel's recommendations that all nasal drops, sprays, and jellies, and propylhexedrine in inhalant form be labeled to limit use to not more than 3 days so as to discourage prolonged use and that a doctor should be consulted if symptoms persisted after 3 days of use. (See § 341.80 (c)(2)(iii)(*a*) and (c)(2)(vi) in 50 FR 2220 at 2239.) The ingredient l-desoxyephedrine in inhalant form had to bear the same warning except it stated 7 days instead of 3 days. (See § 341.80(c)(2)(ii) and discussion in 50 FR 2220 at 2225.)

In addition, the agency has reviewed comments to the Cough-Cold Panel's report concerning rebound congestion and finds seven comments from allergists who specifically mentioned oxymetazoline, xylometazoline, naphazoline, or phenylephrine as causing rebound congestion due to prolonged or excessive use (Ref. 1). Moreover, the agency has reviewed adverse drug reaction reports for the years 1976 to 1993 and finds that the two most frequently reported adverse effects of marketed OTC topical nasal decongestant drug products are rebound congestion and drug dependence (Ref. 2).

The agency believes that the OTC availability of topical nasal decongestants is beneficial to many consumers who seek temporary relief from nasal congestion and concurs with the Cough-Cold Panel's recommendations that these products can be safely used according to label directions. The agency is concerned, however, in view of comments submitted to this rulemaking and adverse drug reactions reported to FDA, that consumers may not be adequately alerted and warned of the problem of rebound congestion, which may be caused by prolonged or excessive use of these preparations. Thus, the agency believes that the 3-day use warning should be expanded to explain to consumers the reason for the 3-day limitation for use of topical nasal decongestants.

Therefore, in this final monograph the warning in § 341.80(c)(2)(iii)(A) for adults, in § 341.80(c)(2)(viii) for children under 12 years of age, and in § 341.80 (c)(2)(v) and (c)(2)(ix) for propylhexedrine in inhalant form for adults and children, respectively, is expanded as follows: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

The agency concludes that these additions to the labeling included in this final monograph will provide for the safe and effective use of OTC topical nasal decongestant drugs.

References

(1) Comments No. C0026, C0077, C0092, C0095, C0118, C0120, C0130, Docket No. 76N–0052, Dockets Management Branch.

(2) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports: Nasal–76–93," 1976–1993, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

3 Referring to the statements in the tentative final monograph for OTC antihistamine drug products, "* * * antihistamines did not reduce nasal obstruction and therefore did not aid in sinus drainage. To the contrary, the studies indicated that antihistamines may sometimes further aggravate nasal obstruction" (50 FR 2200 at 2203), one comment expressed concern that FDA not use this statement as a basis for disagreeing with the Cough-Cold Panel's Category I classification of combinations containing an antihistamine and an oral nasal decongestant.

In the tentative final monograph for OTC antihistamine drug products (50 FR 2200 at 2203), the agency made the statements quoted above as part of its discussion that antihistamines are ineffective for the treatment of sinus congestion. It was not the agency's intent to use the statements as a basis for disagreeing with combination drug products containing an antihistamine and an oral nasal decongestant.

In the tentative final monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products, the agency agreed with the Cough-Cold Panel's Category I classification of combinations containing an antihistamine and an oral nasal decongestant (53 FR 30522 at 30539). In view of the data reviewed by the Cough-Cold Panel that support combinations containing an antihistamine and an oral nasal decongestant (41 FR 38312 at 38326) and the extensive data on such combinations that are available to the agency, the agency reiterates the Cough-Cold Panel's recommendation that combinations containing an antihistamine and an oral nasal decongestant are safe, effective, and rational.

B. Comments on Switching Prescription Nasal Decongestant Active Ingredients to OTC Status

4. Several comments opposed the availability of oxymetazoline hydrochloride and xylometazoline hydrochloride as OTC topical nasal decongestants. The comments also opposed the availability of pseudoephedrine hydrochloride and pseudoephedrine sulfate at dosage levels twice as high as previously permitted for OTC use. The comments expressed concern that these drugs could be dangerous or harmful to many people, young and old alike. One comment felt that self-medicating with nasal decongestants might cause damage to "mucous-lined passages" and that consumers might not know if they have one of the conditions (i.e., heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland) listed in the warnings for these

products. Two comments approved of FDA's requirement for warning information in labeling and supported the OTC availability of these drugs. Another comment mentioned, however, that many persons unfortunately do not or cannot read labels.

As discussed in the tentative final monograph, the agency reviewed safety and effectiveness data on oxymetazoline hydrochloride, xylometazoline hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate and agreed with the Cough-Cold Panel that these active ingredients could be generally recognized as safe and effective for OTC use when appropriately labeled. (See 50 FR 2220 at 2222 to 2223, 2229 to 2230, and 2233 to 2234.) The comments did not submit any data to show that these ingredients should not be available OTC.

To enhance the safe use of these ingredients, in the tentative final monograph, the agency modified several of the Cough-Cold Panel's recommendations regarding pseudoephedrine hydrochloride and pseudoephedrine sulfate as oral nasal decongestants, and oxymetazoline hydrochloride and xylometazoline hydrochloride as topical nasal decongestants. For example, the agency reduced the maximum adult oral dosage of pseudoephedrine preparations from 360 milligrams (mg) to 240 mg in 24 hours (50 FR 2229 to 2230). The agency also proposed that topical nasal decongestant products containing oxymetazoline hydrochloride and xylometazoline hydrochloride not be used in children under 6 years of age unless recommended by a doctor (50 FR 2222 to 2223).

Regarding one comment's concern that self-medicating with OTC nasal decongestants might cause damage to "mucous-lined passages," the comment did not explain its use of the term "mucous-lined passages," nor did it submit any data to substantiate its claim that OTC nasal decongestants at the recommended dosages can cause damage to "mucous-lined passages." Although frequent and prolonged use of topical nasal decongestants may lead to rebound congestion (see comment 2 in section I.A. of this document), the agency is unaware of possible long-term damage to "mucous-lined passages" if a topical nasal decongestant drug product is used for a short period of time and according to directions. As the Cough-Cold Panel pointed out, the problem of rebound congestion is not a factor with use of the orally administered nasal decongestants (41 FR 38312 at 38397).

Regarding the comment's concern that consumers might not know if they have one of the conditions listed in the warnings for these products (i.e., heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland), the agency notes that there are additional warnings in the monograph informing consumers that topical nasal decongestants should not to be used for more than 3 days and that oral nasal decongestants should not be used for more than 7 days, and if symptoms persist, to consult a doctor. Because these products are intended to be used for a limited time only, the agency believes that the risk of adverse effects at the recommended oral or topical dosages is minimal. Moreover, the agency believes that persons having most of the conditions listed in the warning (heart disease, thyroid disease, diabetes, difficulty in urination) would be aware of their condition (because of other apparent symptoms) and be under medical treatment, and the warning instructs them not to use the product unless directed by a doctor.

There is a concern, however, for individuals having certain conditions that may have no apparent symptoms. High blood pressure is a well-known example of such a disease. Persons with high blood pressure may be unaware that they have the condition and may use a nasal decongestant without being aware that the nasal decongestant drug can affect the condition. Nasal decongestants and other sympathomimetic drugs can produce a variety of adverse effects and should be used with caution in individuals with high blood pressure (Refs. 1 and 2). Of the estimated 58 million hypertensive individuals in the United States, about 20 percent (approximately 11 million) do not know they have high blood pressure (Ref. 3). If high blood pressure is not treated, problems such as heart failure, stroke, and kidney disease may occur. The agency believes that periodic medical examinations, high blood pressure screening programs, and education are the most important tools to detect undiagnosed hypertensive individuals. The agency encourages consumers to take advantage of such programs to help minimize the risks associated with undiagnosed high blood pressure.

Regarding the comment that many persons unfortunately do not or cannot read labels, the agency notes that section 502(c) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(c)) requires that a drug be labeled "* * * in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use." The labeling in this final monograph is intended to meet this statutory requirement.

The safety and effectiveness data on oxymetazoline hydrochloride, xylometazoline hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate that were reviewed by the Cough-Cold Panel and the agency support the agency's conclusion that these ingredients can be generally recognized as safe and effective for OTC use when marketed in accordance with the labeling and other conditions established in this final monograph.

References

(1) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, p. 192, 1992.

(2) "Drug Evaluations Annual," American Medical Association, Milwaukee, WI, pp. 407–408, 1991.

(3) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, p. 419, 1992.

C. Comments on Specific OTC Nasal Decongestant Active Ingredients

5. One comment requested that the agency place camphor (0.1 percent), eucalyptus oil (0.025 percent), and menthol (0.05 percent) in Category I as individual OTC topical/inhalant nasal decongestants for use in a hot steam vaporizer; and place the ingredients camphor (4.73 to 5.3 percent), eucalyptus oil (1.2 to 1.3 percent), and menthol (2.6 to 2.8 percent) in Category I as individual OTC topical/inhalant nasal decongestants for use in a chest rub ointment form. The comment submitted three controlled clinical studies (CRD 83–10, CRD 82–10, and CRD 82–09) and two pilot clinical studies (CRD 74–63A and CRD 75–39) of the individual ingredients to support its request (Ref. 1). The first study (CRD 83–10) concerned the single aromatics in steam from a vaporizer. The other four studies concerned the single aromatics in petrolatum applied to the chest and throat. In response to the agency's concerns regarding the statistical analysis of study CRD 83–10 (Ref. 2), the comment provided a statistical reanalysis of the study (Ref. 3).

The agency has reviewed the data and determined that the clinical studies do not support the reclassification of the individual ingredients as requested by the comment. Although one study (CRD 83–10) shows some statistically significant evidence of the effectiveness of camphor, eucalyptus oil, and menthol as topical/inhalant nasal decongestants administered by steam vaporization, there are certain statistical problems

with the data that make the results questionable. Although the statistical reanalysis provides some statistical evidence of efficacy, the agency concludes that stronger evidence of efficacy from a second study is needed (Ref. 4). The other four studies (CRD 82–10, CRD 82–09, CRD 74–63A, and CRD 75–39) are insufficient to demonstrate the effectiveness of camphor, eucalyptus oil, and menthol as individual topical/inhalant nasal decongestants in a chest rub ointment form.

Study CRD 83–10 was designed to determine the individual topical/inhalant nasal decongestant effect of camphor, eucalyptus oil, and menthol vaporized in steam compared to unmedicated steam. In this single-blind, parallel study, 234 subjects with acute upper respiratory tract infection were equally divided into 4 treatment groups (vaporized camphor, eucalyptus oil, menthol, or steam control). Nasal airway resistance was measured with a rhinomanometer before treatment, every 15 minutes (min) for the first hour and every 30 min for the second hour. The investigator reported that when the individual observation time points were examined, the results indicated that each ingredient was significantly more effective in reducing nasal congestion than steam alone at each 15-min interval over the first hour (all $p \leq 0.02$) and over the entire 2-hour exposure period.

Although the comment claimed that study CRD 83–10 showed each active ingredient to be statistically better than placebo (steam) control, the agency has determined that the data and the reanalysis of study CRD 83–10 alone do not provide adequate support for the monograph status of camphor, eucalyptus oil, and menthol as individual topical/inhalant nasal decongestant ingredients for several reasons. First, there was an improper use of baseline values; for example, the baseline values were measured 15 min and 0 min before treatment, but only the 0-minute measurement was used as the baseline value. Conversely, in study CRD 82–10, the baseline values were taken as the average of 15- and 0-min pretreatment measurements. Second, the use of the Bartlett's test to verify the assumption of homogeneity of the variances in the logarithm-transformed data demonstrated that the homogeneity of the variances was found to be acceptable for only the first 60 min, i.e., variances among treatment groups were not significantly different for the periods of 15, 30, 45, and 60 min. However, statistically significant differences were found at 90 min, 120 min, and overall, with the steam control group showing an unacceptable consistently higher variance than the active ingredient treatment groups. Third, the reanalysis of the logarithm-transformed rhinomanometer measurement data by the Kruskal-Wallis test (a nonparametric test) showed that the active ingredients were statistically better than the steam control group only within the first hour of the study and not significantly better than the steam control group after one hour. These weak findings would be further weakened if adjustment for p-value for multiple testing of time points were made.

Should another study be done, a repeated measurement analysis (i.e., an overall analysis) of the rhinomanometer data needs to consider the increase in variance over all time points to remedy the problem of repeated testings. Further, if variances in results increase over the time period in an additional study, the reason for this occurrence needs to be addressed.

Study CRD 82–10 compared the nasal decongestant effects of the individual ingredients camphor 5.2 percent, eucalyptus oil 1.3 percent, and menthol 2.8 percent in petrolatum against a petrolatum placebo in 40 subjects per group with acute coryzal rhinitis (common cold) using a randomized parallel design. The investigator reported that there were no statistically significant differences between treatments with respect to objectively measured nasal congestion for the total study population. Study CRD 82–09 used the same protocol as CRD 82–10, with 39 to 42 subjects per group. This study also did not show any statistically significant differences between test and control treatments. In conclusion, both studies, CRD 82–10 and CRD 82–09, provide no statistically significant data that the individual active ingredients were better than petrolatum control in reducing nasal congestion in subjects with acute coryzal rhinitis.

Regarding the two pilot studies (CRD 74–63A and CRD 75–39), the agency notes that both studies used the same protocol. The studies were randomized crossover studies using subjects with colds. Comparisons were made by objective measurement of nasal airway resistance using anterior rhinomanometry. Study CRD 74–63A compared a commercial product containing a combination of volatile aromatic oils with the following individual ingredients: Eucalyptus oil 1.33 percent in a petrolatum base, turpentine oil 5.12 percent in a petrolatum base, and petrolatum (placebo). Study CRD 75–39 compared the nasal decongestant effects of a commercial product containing a combination of volatile aromatic oils with the following individual ingredients: Camphor 4.7 percent in a petrolatum base, menthol 2.6 percent in a petrolatum base, and petrolatum (placebo). A summary statistical analysis of studies CRD 74–63A and CRD 75–39, prepared by the comment's statistician (Ref. 2), states that these studies show no statistical advantages for the components over petrolatum and that the absence of statistical significance in these studies is not unexpected because of the small sample sizes of the treatment groups. Furthermore, significant residual effects were detected in the data from these studies, indicating that the crossover model was inappropriate. The agency concludes that studies CRD 74–63A and CRD 75–39 do not provide adequate data to demonstrate the effectiveness of camphor, eucalyptus oil, and menthol as individual topical/inhalant active ingredients when administered in a chest rub ointment form.

In conclusion, the submitted data are insufficient to generally recognize camphor, eucalyptus oil, and menthol as safe and effective as individual topical/inhalant nasal decongestant active ingredients, either in petrolatum applied to the chest and throat or in a hot steam vaporizer. Therefore, at this time, these ingredients for these uses are not being included in the final monograph for OTC nasal decongestant drug products. Combination products containing these ingredients are discussed in the tentative final monograph for OTC cough-cold combination drug products, published in the **Federal Register** of August 12, 1988 (53 FR 30522). In that tentative final monograph nasal decongestant use was discussed in comment 59 (53 FR 30522 at 30550), and antitussive use was discussed in comments 56 and 57 (53 FR 30522 at 30547 to 30548). These combination products will be addressed in the final monograph for OTC cough-cold combination drug products, which will be published in a future issue of the **Federal Register.**

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) "VapoRub," Vol. 1, Richardson-Vicks, Inc., submitted as part of Comment No. C0212, Docket No. 76N–052N, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to E. J. Hanus, Richardson-Vicks, Inc., coded as LET095, Docket No. 76N–052N, Dockets Management Branch.

(3) Letter from E. J. Hanus, Richardson-Vicks, Inc., to W. E. Gilbertson, FDA, coded as LET096, Docket No. 76N–052N, Dockets Management Branch.
(4) Letter from W. E. Gilbertson, FDA, to E. J. Hanus, Richardson-Vicks, Inc., coded as LET109, Docket No. 76N–052N, Dockets Management Branch.

6. One comment submitted data (Refs. 1 and 2) to support the effectiveness of ephedrine and its salts as an oral nasal decongestant. The data consisted of four studies (CRD 78–04, CRD 78–06, CRD 78–26, and CRD 78–27) (Refs. 3 through 6) in which the data were pooled and analyzed as one study; three single-investigator studies (CRD 74–9, CRD 74–57, and CRD 76–61) (Refs. 7, 8, and 9); and four articles from the scientific literature (Refs. 10 through 13). Additional statistical information (Ref. 2) was provided by the comment in response to the agency's request (Ref. 14). The comment also noted that the agency concluded in the tentative final monograph for OTC bronchodilator drug products (47 FR 47520 at 47527, October 26, 1982) that ephedrine and its salts at a 25-mg oral dose as a bronchodilator are safe for OTC use. The comment requested that ephedrine and its salts be placed in Category I for oral nasal decongestant use at a dosage of 8 to 25 mg every 4 hours, not to exceed 75 mg in 24 hours.

The pooled study (studies CRD 78–04, CRD 78–06, CRD 78–26, and CRD 78–27) (Refs. 3 through 6) involved a total of 445 subjects obtained by 4 different investigators. These were parallel studies with 60 subjects participating in CRD 78–04, 54 subjects in CRD 78–06, 202 subjects in CRD 78–26, and 129 subjects in CRD 78–27. Each study group was subdivided into three subgroups. The subjects in each subgroup received a single dose of aqueous solution containing ephedrine sulfate 8 mg/dose, ephedrine sulfate 12 mg/dose, or an aqueous placebo. Nasal airway resistance was measured by Vick's Rhinomanometer at 30, 60, 90, 120, and 180 min after the dose was given.

In analyzing the data in the pooled study, the agency noted that out of the four studies, there were only sporadic statistically significant rhinomanometer data differences in favor of ephedrine 12 mg over placebo in Study CRD 78–26 (Ref. 5). For subjective subject ratings of nasal congestion, there were only sporadic statistically significant differences in favor of ephedrine 12 mg over placebo in Study CRD 78–26. With sample sizes ranging from 17 to 45 subjects per treatment group, there should be adequate statistical power to detect a significant clinical difference if it exists. However, both rhinomanometer measurements and subject ratings of nasal congestion data failed to clearly differentiate ephedrine from placebo in these studies.

In the pooled data analysis, significant treatment by center interaction was found in 3 of the 5 time-point analyses ($p \leq 0.15$). Six of 25 time-point analyses (24 percent) showed that placebo was the same or better than ephedrine. A statistical reanalysis of the data (Ref. 2) did not establish any statistical evidence, either in the pooled data or in any of the individual studies, that ephedrine is superior to the placebo control in reducing nasal congestion. The agency also notes that this reanalysis of the data using the Kruskal-Wallis test (a nonparametric version of "one-way" analysis of variance) does not remove the issue of center interaction. Further, the mathematical model that was used to analyze the rhinomanometer data provides an extremely low R-square value. Hence, the agency considers these findings as casting doubt on the poolability of these efficacy data and believes that conclusions should be drawn based on the results from individual studies. Therefore, the agency concludes that the data in the pooled study fail to provide substantive statistical evidence of effectiveness.

The single-investigator studies (CRD 74–9, CRD 74–57, and CRD 76–61) (Refs. 7, 8, and 9) involved a total of 316 subjects. Study CRD 74–57 (Ref. 8) did not show any statistically significant difference between ephedrine and placebo. This parallel-design, double-blind, computer-randomized study used nasal airway flow rate measurements to compare the nasal decongestant effect of solutions of ephedrine sulfate 8 mg/30 milliliters (mL), ephedrine sulfate 16 mg/30 mL, phenylpropanolamine hydrochloride 37.5 mg/30 mL, and a 30 mL placebo vehicle solution containing no active ingredient. Two doses were given, 4 hours apart. A total of 189 subjects with nasal congestion due to coryza was divided among the 4 treatment groups. The results showed that the phenylpropanolamine solution had the greatest effect on increasing nasal airflow when compared with both doses of ephedrine and the placebo. Both doses of ephedrine produced significantly greater flow than placebo overall, but not at any of the individual time intervals. The effect of ephedrine 16 mg/30 mL also approached significance at the final evaluation (2 hours after the second dose). There were no significant differences noted in the subjective evaluation of runny nose, post-nasal drip, watery eyes, and number of sneezes. However, the use of the ephedrine 16 mg/30 mL solution seemed to be beneficial in reducing the number of "nose blows."

Study CRD 74–9 (Ref. 7) also did not demonstrate any statistically significant difference between ephedrine and placebo. This was a parallel-design study employing 86 subjects with nasal congestion due to coryza. The subjects were divided into 3 subgroups with 29 subjects receiving ephedrine sulfate 8 mg/30 mL (aqueous vehicle), 29 subjects receiving phenylpropanolamine hydrochloride 25 mg/30 mL (aqueous vehicle), and 28 subjects receiving 30 mL of the aqueous vehicle alone. It was noted in this study that sorbitol was added to the test solution given to the first 34 subjects. However, when 3 subjects (1 in each of the 3 treatment groups) experienced intestinal distress, the remaining 52 subjects were given an aqueous test solution without the sorbitol. The agency notes that, in general, no clinical conclusions can be derived from this study because of the differing results obtained between the sorbitol and nonsorbitol-containing test solutions.

Only one study, CRD 76–61 (Ref. 9), showed some favorable results. This study was a double-blind, computer-randomized crossover study involving 41 subjects having nasal congestion due to coryza. Eighteen subjects received 8 mg of ephedrine sulfate and 23 subjects received 12 mg of ephedrine sulfate on one of two test days, both administered in 30 mL of aqueous vehicle. All 41 subjects received aqueous vehicle placebo on the other test day. Nasal airway resistance was used as an objective measure of nasal congestion and changes therein. Resistance was measured by Vick's Rhinomanometer before treatments were administered and at 30, 60, 90, 120, and 180 min after treatments, which were 24 hours apart. Subjective ratings were also recorded before each measurement. Subjectively, subjects using the 8-mg and 12-mg doses of ephedrine sulfate perceived an improvement in nasal decongestion to a statistically significant extent, but the comparisons with placebo results were not significant. As determined by nasal airway resistance measurements, both the 8-mg and 12-mg doses of ephedrine sulfate decreased the nasal congestion of subjects to a statistically significant extent overall, in comparison with the results obtained with the placebo. However, the agency considers the results of the study to be inconsistent because the ephedrine 8-mg group obtained some favorable results over placebo at 60 min after treatment, but the ephedrine 12-mg group obtained

only sporadically favorable results. In addition, the 12-mg group obtained significant results only within the first hour after treatment, while the 8-mg group did not obtain significant results until 1 hour after treatment. These discrepancies are not adequately explained. The agency believes that the findings in both the pooled studies (Refs. 3 through 6) and the individual study CRD 76–61 (Ref. 9) would be further weakened if adjustments for multiple testings of hypotheses were made.

With regard to the four articles (Refs. 10 through 13) from the literature, the agency finds that these articles are not supportive of either the pooled study or the individual studies. The McLaurin, Shipman, and Rosedale study (Ref. 10) was reviewed by the Cough-Cold Panel, which found that it did not contain any conclusive data to support claims of nasal decongestant effectiveness for 8 to 12 mg ephedrine doses contained in OTC drug products (41 FR 38312 at 38408). Although the Cough-Cold Panel stated that the study demonstrated nasal decongestant effectiveness of orally administered ephedrine sulfate in doses of 25 mg, the agency considers the study inadequate to establish effectiveness because it was not controlled. The study by Gowen and Nedzel (Ref. 11) and the study by Mothersill (Ref. 12) are not adequate because the results were subjective and ephedrine was not studied alone, but in combination with other active ingredients. Likewise, the Aschan study (Ref. 13) also was not a single active ingredient study.

Although safety is not a problem, as the comment noted, based on the lack of adequate data to demonstrate effectiveness, ephedrine and its salts are not being included as oral nasal decongestant ingredients in this final monograph. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 15).

References

(1) Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(2) Comment No. SUP003, Docket No. 76N–052N, Dockets Management Branch.
(3) Hayes, S.L., "Multicenter-Pooled Study," draft of unpublished study (CRD 78–04), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(4) Fulco, O.J., "Multicenter-Pooled Study," draft of unpublished study (CRD 78–06), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(5) doPico, G.A., "Multicenter-Pooled Study", draft of unpublished study (CRD 78–26), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(6) Diamond, P.H., "Multicenter-Pooled Study," draft of unpublished study (CRD 78–27), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(7) Connell, J.T., "Ephedrine, Phenylpropanolamine, and Placebo Comparisons," draft of unpublished study (CRD 74–9), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(8) Connell, J.T., "Nasal Airway Flow Rate Measurement Comparisons," draft of unpublished study (CRD 74–57), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(9) doPico, G.A., "Ephedrine and Placebo Comparison," draft of unpublished study (CRD 76–61), in Comment No. C0214, Docket No. 76N–052N, Dockets Management Branch.
(10) McLaurin, J.W., W.F. Shipman, and R. Rosedale, "Oral Decongestants—A Double Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective," *Laryngoscope*, 71:54–67, 1961.
(11) Gowen, G.H., and A.J. Nedzel, "Effectiveness of the Oral Administration of Ephedrine in the Common Cold," *Illinois Medical Journal*, 71:132–136, 1937.
(12) Mothersill, M.H., "Treatment of Hay Fever with a Combination of a Sympathomimetic and an Antihistaminic Drug," *Annals of Allergy*, 8:223–228, 1950.
(13) Aschan, G., "Decongestion of Nasal Mucous Membranes by Oral Medication in Acute Rhinitis," *Acta Otolaryng*, 77:433–438, 1974.
(14) Letter from W.E. Gilbertson, FDA, to E.J. Hanus, Richardson-Vicks, coded LET020, Docket No. 76N–052N, Dockets Management Branch.
(15) Letter from W.E. Gilbertson, FDA, to E.J. Hanus, Richardson-Vicks, coded LET107, Docket No. 76N–052N, Dockets Management Branch.

7. One comment submitted a citizen petition requesting that 10 mg menthol in a solid dosage form for use as a topical/inhalant nasal decongestant be included in the final monograph (Refs. 1 and 2). The comment requested the following directions for use for the 10-mg menthol solid dosage form: "Adults and children 3 to under 12 years of age: dissolve one solid dosage form in the mouth every 2 hours as needed. Do not chew. Children under 3 years of age: consult a doctor."

The agency has reviewed the petition and other information and finds the data supportive of the effectiveness of a 10-mg menthol lozenge as a single dose for topical nasal decongestant use. However, the agency has concluded that the data are not sufficient to include the ingredient in the monograph for the reasons discussed below.

The petition included a double-blind, randomized, placebo-controlled, parallel-design, single-dose study of a 10-mg menthol lozenge in subjects with viral rhinitis. The subjects were at least 18 years of age with symptoms of stuffy nose, runny nose, sneezing, and/or cough of no more than 48 hours duration. The objective of the study was to determine if statistically significant decreases in nasal airway resistance occurred at specific intervals after administration of the drug. Posterior rhinometry measurements were correlated with the subjects' subjective ratings of decongestant activity. Measurements of nasal flow/resistance were made 5 min before and immediately prior (0 min) to administration of the test lozenge and at 15, 30, 60, 90, and 120 min after dosing. The measurement immediately prior to dosing was used as the baseline measurement. The nasal/flow resistance data were analyzed by a repeated measures analysis of variance with 6 time points (baseline, 15, 30, 60, 90, and 120 min) as the repeat factor. Changes from the baseline at the post-treatment time points were also analyzed using a one-way analysis of variance.

The agency notes that the protocol for this study is similar to that proposed by the Panel (41 FR 38312 at 38415). The Cough-Cold Panel recommended that a study to show effectiveness of a nasal decongestant drug should be a double-blind, placebo-controlled assessment of the drug's ability to decrease nasal airway resistance. The Cough-Cold Panel also considered subjective assessment by the subjects to be desirable. The Cough-Cold Panel stated that where rebound congestion with repeated use is a concern, labeling should specify short-term use in providing temporary relief of symptoms. The Cough-Cold Panel recommended that specific data be obtained by testing the nasal decongestant in the concentrations and maximal dosage frequencies to be recommended for periods of at least 1 week to address the incidence and severity of a drug-induced increase in nasal airway resistance. The Cough-Cold Panel required two positive studies based on the results of two different investigators or laboratories to show effectiveness.

The agency finds that the results of the study suggest that 10 mg menthol in a solid dosage form is effective in the relief of nasal congestion due to viral rhinitis. However, the repeated measures analysis of variance results were not informative because they

included the baseline levels in the analysis. By deleting the baseline levels from the analysis, the agency notes that the multivariate analyses of the data using the Statistical Analysis System Institute statistical system showed a significant treatment effect but nonsignificant time and treatment by time interaction. The results of the study support a 2-hour duration of action from a single dose. However, because the proposed directions for the product include multiple doses (i.e., "every 2 hours as needed"), another study involving multiple doses is needed to support effectiveness. The study needs to be done using the same dosage with the drug given at the same time intervals as proposed for the label directions. A 3-day study is necessary to show effectiveness as a nasal decongestant if the product will be indicated for colds and 7 days if indicated for allergies.

The agency notes that the petition did not address the potential problem of rebound congestion occurring with repeated use of menthol lozenges. In the tentative final monograph (50 FR 2220 at 2233), the agency discussed the occurrence of rebound congestion resulting from topical nasal decongestants in a lozenge or mouthwash dosage form. The agency stated that when ingredients such as menthol are administered in the form of lozenges, rebound is unlikely to occur and that it may be more appropriate to use a 7-day warning, i.e., "Do not use this product for more than 7 days," rather than a 3-day warning. However, because such lozenges are not included in this final monograph, such a warning requirement is not applicable at this time. The agency believes that the potential for rebound congestion to occur should be studied in any multi-dose study, such as the study discussed above, involving topical nasal decongestants in a lozenge or mouthwash dosage form to rule out the potential for rebound congestion to occur and to determine which warning statement would be appropriate to use for the product.

Based on the above information, the agency is not including 10 mg menthol in solid dosage form as a topical nasal decongestant in this final monograph. The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) Comment No. CP00010, Docket No. 76N–052N, Dockets Management Branch.

(2) Letter from C.A. Sloughfy, Jr., Beecham Products, to J.R. Gebert, FDA, coded as LET101, Docket No. 76N–052N, Dockets Management Branch.

(3) Letter from W.E. Gilbertson, FDA, to B. Misek, Beecham Products, coded as LET108, Docket No. 76N–052N, Dockets Management Branch.

8. One comment objected to the agency's proposal in the tentative final monograph to restrict to professional labeling the use of oxymetazoline hydrochloride in children under 6 years of age because this action would exclude such use from general consumer labeling. Referring to studies that showed substantial differences when oxymetazoline was given to dogs intranasally and intravenously to elicit a cardiovascular effect (i.e., increase in blood pressure), the comment stated that the amount of oxymetazoline required to elicit any systemic effect by the intranasal route would be virtually unachievable with marketed products. Thus, according to the comment, it would be extremely unlikely that a child could receive a dose of oxymetazoline that would have systemic effects. In addition, the comment stated that a review of the company's adverse experience files showed no cardiovascular side effects from oxymetazoline that were not associated with significant overuse (either in frequency of use, quantity of use, or both). The comment added that a tabulation of the company's and FDA's adverse reaction files for oxymetazoline for the period 1975 to 1989 showed only three cases of adverse reactions in children. The comment stated that the scarcity of adverse reaction experiences demonstrates that there is no safety problem. Further, the comment contended that limiting pediatric formulations (0.025 percent) of oxymetazoline to professional labeling (excluding use from consumer labeling) is inappropriate because an OTC drug must first be available to consumers with proper labeling before professional labeling can apply. The comment contended that the agency's justification for placing 0.025 percent oxymetazoline in professional labeling, i.e., that there is a theoretical possibility of a young child swallowing excessive amounts of a potent long-acting drug due to difficulty in administering accurate dosages, is unfounded. The comment stated that if this problem does exist, it would also be a problem with the shorter acting topically applied nasal decongestant drug products because these shorter acting drug products are administered more often. If this is the case, according to the comment, then the shorter acting drug products labeled for use in young children should be labeled with the same age restrictions as proposed for oxymetazoline.

With respect to the agency's concern that it is difficult to measure the correct dose in a small child and that the child may receive an excessive dose by swallowing the administered medication (50 FR 2220 at 2230), the comment contended that drops are more easily administered than sprays. The comment stated that drops are sufficiently accurate to assure safe use in children and that, to the best of its knowledge, all pediatric formulations (0.025 percent) of oxymetazoline are marketed for use as drops, not sprays. The comment noted, specifically, that the orifice of the dropper of its oxymetazoline pediatric nasal drops drug product is controlled so that it consistently delivers an average drop volume of 0.028±0.008 mL. The comment argued that this additional safety feature further assures the accuracy of the dose. The comment concluded that it is extremely unlikely that a child could receive a dose of oxymetazoline that would have a systemic effect, even if the child inadvertently swallowed some of the drops.

The comment maintained that restricting pediatric use of oxymetazoline to professional labeling will not ease the task of measuring a correct dose, nor will it cause a young child to swallow any less of a nasal solution than he/she otherwise would. The comment contended that dosing concerns can be addressed by consumer labeling. For example, instructions for use in children might include a provision that if less than a full dose is delivered on the first try, no further attempt to readminister the drug should be made. Additionally, an alternative safeguard could be provided by restricting the amount of drug that a dropper can deliver, i.e., a safety dropper can be designed to deliver approximately 6 drops which corresponds to the labeled maximum dose of 3 drops in each nostril under conditions of normal use. The comment concluded that the agency should accept the Panel's recommendation to permit consumer labeling for oxymetazoline for children 2 to under 6 years of age.

The agency has reviewed its adverse reaction reports for oxymetazoline covering the period from 1969 to the present (Ref. 1). Only five adverse reactions in children under 8 years of age have been reported. Six adverse reactions involving xylometazoline in children under 8 years of age have been reported to the agency since 1970 (Ref.

2). Except for a single death (without sufficient detail to attribute cause in a 3-month-old male who presented a history consistent with sudden infant death syndrome), all affected children recovered soon after discontinuation of the medication. The reported reactions are generally of expected events (i.e., excitation, agitation) or involve concomitant medications associated with the reactions (e.g., antihistamines and sleepiness, or a previous history of rash from an antibiotic). Considering the long marketing history and the extent of the use of topical oxymetazoline and xylometazoline, the agency considers the number and severity of the reported cases to be very low.

Biesalski and Marquart (Ref. 3) evaluated the nasal decongestant effect of xylometazoline hydrochloride (0.1 and 0.01 percent) in 72 infants aged 5 days to 14 months, 3 premature infants, and 42 children. An additional group of 48 infants was given xylometazoline in concentrations ranging from 0.0005 to 0.005 percent. The investigators measured blood pressure in 11 children and monitored cardiac activity in 69 infants and found no effects caused by the drug. Four infants with congenital heart defects had no side effects on the heart or circulation from the drug. The investigators stated, "No side effects of any kind were noted, even in premature infants or in infants with cardiac conditions."

Based on this safety profile and the ability to control the amount of drug administered per drop or spray, the agency concludes that limiting information on the topical use of oxymetazoline and xylometazoline in children 2 to under 6 years of age to professional labeling only is unwarranted. This type of limitation would not eliminate the dangers of misuse and overuse in this age group. The agency agrees with the comment that the risk of overdose or misuse can be adequately handled by the use of a dropper or spray that is designed to restrict the amount of drug delivered to a maximum allowable dose and by appropriate OTC labeling directions and warnings.

The United States Pharmacopeia discusses calibrated dropper specifications where accuracy of dosage is important. The volume error incurred in measuring any liquid by means of a calibrated dropper should not exceed 15 percent under normal use conditions (Ref. 4). The agency is incorporating this standard for a calibrated dropper in the final monograph. The agency believes that this criterion will help assure an accurate dose and minimize the risk of overdose.

To further emphasize to consumers the importance of proper administration and the dangers of overdose in children in this age group, the agency is incorporating the following statement in the directions: "Use only recommended amount." The agency recognizes that the warnings for these two drugs already include the statement "Do not exceed recommended dosage." Nonetheless, the agency believes that an additional statement in the directions sections will reinforce the importance of not using an excessive amount of drug. The agency also believes that the warning not to exceed the recommended doses within a 24-hour period will provide an additional safeguard against overdosing. The agency is requiring that both of these statements appear in product labeling in boldface type.

Accordingly, the agency is adding new sections for oxymetazoline hydrochloride (§ 341.80(d)(2)(iv)(A)(*2*)) and xylometazoline hydrochloride (§ 341.80(d)(2)(vii)(A)(*2*)). The agency is requiring that pediatric products be marketed in a container with a controlled, metered-dose children's safety dropper or spray that is calibrated to deliver no more than a maximum allowable dose. Based on the information on the controlled dropper provided by the comment, which is the manufacturer of the major marketed OTC oxymetazoline pediatric nose drop products, the following doses are being included in this final monograph.

For oxymetazoline hydrochloride, the product must have either a calibrated dropper or a metered-dose spray that delivers no more than 0.027 mg of oxymetazoline hydrochloride per three drops or three sprays. The directions for use are to include the following information: Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril of a 0.025-percent aqueous solution not more often than every 10 to 12 hours. Use only recommended amount. Do not exceed 2 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

For xylometazoline hydrochloride, the product must have either a calibrated dropper or metered-dose spray that delivers no more than 0.054 mg of xylometazoline hydrochloride per three drops or three sprays. The directions for use are to include the following information: Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril of a 0.05-percent aqueous solution not more often than every 8 to 10 hours. Use only recommended amount. Do not exceed 3 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

Phenylephrine 0.125 percent aqueous solution is the only other OTC topical nasal decongestant labeled for use by children 2 to under 6 years of age. The agency believes that products containing this drug should also have a calibrated dropper or a metered-dose spray. Using the same standard as above, the product must have either a calibrated dropper or metered-dose spray that delivers no more than 0.135 mg per three drops or three sprays. Similarly, the directions for use are to include the following statement: "Use only recommended amount."

If manufacturers have information that demonstrates that an amount of drug different than those listed above for three drops or sprays of oxymetazoline hydrochloride, xylometazoline hydrochloride, and phenylephrine hydrochloride, the agency will evaluate that information and determine if the above standards should be changed. Manufacturers should submit the information in a citizen petition in accord with § 10.30 (21 CFR 10.30).

References

(1) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports," 1969–1993.

(2) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports," 1970–1993.

(3) Biesalski, P., and K. Marquart, "Therapeutic Aspects of Rhinitis in Early Childhood, Thermoelectrode Investigations with Nasal Decongestants" ("Zur Behandlungder Rhinitis im fruhen Kindesalter. Thermoelektrische Untersuchungen an abschwellenden Nasenmittein") (English Translation), *Schweizerische Medizinische Wochenschrift*, 89(19):510–512, 1959.

(4) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1684, 1989.

9. One comment requested that the status of phenylephrine bitartrate be clarified in the final monograph. The comment stated that data were submitted to the Cough-Cold Panel indicating that phenylephrine bitartrate, while not as commonly used as the hydrochloride salt of phenylephrine, had the same characteristics (Refs. 1 and 2). The comment noted that the proposed dose of phenylephrine hydrochloride in adults is 10 mg which is equivalent to approximately 15.5 mg of phenylephrine bitartrate. Stating that the noninclusion of phenylephrine bitartrate in the Cough-Cold Panel's

report and the tentative final monograph appeared to be an inadvertent omission, the comment requested that phenylephrine bitartrate be classified as a Category I oral nasal decongestant.

The agency acknowledges that phenylephrine bitartrate was submitted as an oral nasal decongestant active ingredient in an effervescent combination cold tablet for OTC use containing 7.8 mg phenylephrine bitartrate (4.1 mg phenylephrine base) which is present in the same amount in solution for oral use. The maximum recommended dose is 8 tablets in 24 hours. Therefore, the maximum dose of phenylephrine bitartrate would be 62.4 mg (32.8 mg phenylephrine base) per day (Ref. 1). However, the ingredient apparently was not reviewed by the Cough-Cold Panel or included in its report, or addressed in the tentative final monograph for OTC nasal decongestant drug products. The agency has reviewed the submitted data and notes that the submission (Ref. 1) states that the Physicians' Desk Reference, 1972 edition, lists two products containing phenylephrine bitartrate (Ref. 3). The agency has determined that these two products are aerosol inhalation devices which deliver micronized particles of isoproterenol hydrochloride and phenylephrine bitartrate for inhalation by mouth into the bronchial tree. The products have the following indications: (1) Acute bronchial asthma and other allergic states, and (2) chronic obstructive pulmonary diseases such as chronic bronchitis and pulmonary emphysema (Ref. 3).

The submission also includes an acute oral toxicity study conducted on phenylephrine bitartrate, chlorpheniramine maleate, and phenylephrine hydrochloride as individual active ingredients. The acute oral LD_{50} for phenylephrine bitartrate alone is presented as 170.7 ± 17.0 mg per kilogram (kg); that for phenylephrine hydrochloride alone is presented as 61.3 ± 11.6 mg/kg (Refs. 1 and 2). In addition, the submission includes a bioavailability (blood level) study of phenylephrine bitartrate combined in an effervescent cold tablet with aspirin and chlorpheniramine maleate (Ref. 2). The study compares phenylephrine plasma levels obtained for three combination drug products containing the following active ingredients: (1) Aspirin, phenylephrine bitartrate (7.1 mg), and chlorpheniramine maleate, (2) aspirin, phenylephrine hydrochloride (5 mg), phenindamine tartrate, and caffeine, and (3) phenylephrine hydrochloride (20 mg) and chlorpheniramine maleate. Although comparable plasma levels of phenylephrine were obtained with the first and second test formulations, the agency has determined that these bioavailability studies do not demonstrate effectiveness because the claimed pharmacological effectiveness of OTC drug monograph active ingredients must be established by controlled clinical investigations (21 CFR 330.10(a)(4)(ii)). No clinical data were submitted to show the effectiveness of phenylephrine bitartrate as an oral nasal decongestant. Moreover, the agency has conducted an extensive literature search and is unaware of any data or information in the scientific literature regarding the use of phenylephrine bitartrate as an oral nasal decongestant active ingredient. The products containing phenylephrine bitartrate that were cited by the comment (Refs. 1 and 3) are aerosol products administered by inhalation and are not indicated for nasal decongestant use. Further, the submitted product has been reformulated and no longer contains phenylephrine bitartrate (Ref. 4). The agency concludes that the data are inadequate to generally recognize phenylephrine bitartrate as safe and effective as an oral nasal decongestant, and this ingredient is not being included in the final monograph for OTC nasal decongestant drug products.

References

(1) OTC Vol. 040192.
(2) OTC Vol. 040193.
(3) "Physicians' Desk Reference—1972," 26th ed., Medical Economics, Inc., Oradell, NJ, pp. 1102 and 1105, 1972.
(4) Letter from B.S. Shuster, Miles Laboratories, Inc., to G. Kerner, FDA, dated April 24, 1987, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

10. One comment requested that a product containing phenol 1.56 percent, thymol, sodium perborate, methyl salicylate, alum powder, sage, and honey, used as a spray, atomizer, swab, or gargle, be considered in the nasal decongestant drug products rulemaking. The labeling claim for the product is for "hygienic care of * * * nasal passages" (Ref. 1). In a followup communication with the agency, the comment clarified that phenol is the only active ingredient in the product (Ref. 2).

No data on the use of 1.5 percent phenol for "hygienic care of nasal passages" were submitted to the Cough-Cold Panel following the "call-for-data" notice that was published in the **Federal Register** of August 9, 1972 (37 FR 16029), requesting data on any active ingredients in OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. Nor were any data on phenol for this use submitted to the agency for inclusion in the tentative final monograph for OTC nasal decongestant drug products published in the **Federal Register** of January 15, 1985 (50 FR 2220). Thus, neither the Cough-Cold Panel in its report (41 FR 38312), nor the agency in its tentative final monograph, considered this ingredient or claim for topically applied nasal drugs in the rulemaking for OTC nasal decongestant drug products. The comment did not submit any data to demonstrate the safety and effectiveness of the claimed active ingredient, phenol, in the nasal passages or to substantiate the claim it requested for this ingredient. Nevertheless, the agency has evaluated the claim "hygienic care of nasal passages" and considers this claim to be vague and meaningless because it does not describe any therapeutic benefits to be obtained from use of the product. Thus, the agency concludes that phenol as an active ingredient and labeling for its use "for hygienic care of nasal passages" are nonmonograph conditions.

References

(1) OTC Vol. 160233.
(2) Telephone communications between A. Horn, co-owner of marketing rights for Formula U, and M. Benson, FDA, March 21 and March 30, 1984, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

D. Comments on Dosages for OTC Nasal Decongestant Active Ingredients

11. In response to the agency's proposal (50 FR 2220 at 2229 to 2230) that pseudoephedrine preparations be available at dosage levels twice those previously permitted for OTC use, i.e., 60 mg instead of 30 mg, one comment expressed a hope that pseudoephedrine would continue to be available in 30 mg tablet strength, or if in 60 mg strength, that tablets will be scored for breaking.

The final monograph does not address tablet characteristics such as shape, size, scoring, etc. However, manufacturers must provide consumers with dosage forms and strengths that are consistent with the dosages and directions for use in OTC drug monographs. The adult dosage for products containing pseudoephedrine is 60 mg every 4 to 6 hours. Manufacturers may market a 60-mg product with a one-tablet dosage or a 30-mg product with a two-tablet dosage. The pseudoephedrine dosage for children 6 to under 12 years of age is 30 mg every 4 to 6 hours. Thus, it is reasonable to expect that 30 mg tablets of pseudoephedrine will continue to be available.

12. Several comments recommended that the agency consider new weight-based/age-related pediatric dosing schedules for cough-cold drug products (including nasal decongestants) based on a pediatric dosing unit (PDU) concept that provides for additional age groupings developed to better meet the needs of the growing pediatric patient. Some comments suggested that the Cough-Cold Panel's recommended pediatric dosing schedule of 6 to under 12 years and 2 to under 6 years be replaced with the PDU concept that would utilize a pediatric dosage schedule equivalent to 1/8 the adult dose and include additional age breaks (i.e., 2–3, 4–5, 6–8, 9–10, and 11 years) and/or weight groupings (i.e., 24–35, 36–47, 48–59, 60–71, and 72–95 pounds). Other comments also recommended that this new pediatric dosing schedule be optional. For products targeted primarily for adults, which also incorporate some dosage recommendations for pediatric use, the comments felt that it was reasonable to continue to use the dosing schedule proposed in the tentative final monograph. But for products primarily intended for pediatric use, the comments felt that there was a need for incremental dosing throughout the entire pediatric (under 12 years) age range consistent with the incremental age and weight ranges within the typical growth patterns in children. Stating that the pediatric dosage of cough-cold drug products should be reconciled with the dosage schedules recommended by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel) (42 FR 35346 at 35489 to 35491, July 8, 1977, which includes additional age groupings), two comments contended that such a change would provide consistency between the various monographs and allow for consistency in the formulation of combination drug products containing a nasal decongestant and an analgesic-antipyretic.

Two comments also recommended that the agency add a professional dosing schedule for children under 2 years of age, based on the PDU concept. As an example, one comment suggested that the professional labeling section for oral pseudoephedrine be amended to include the following: Children 1 year of age, 11.25 mg every 4 to 6 hours, not to exceed 45 mg in 24 hours; children 4 months to under 1 year, 7.5 mg every 4 to 6 hours, not to exceed 30 mg in 24 hours.

Because a number of OTC drug rulemakings could be affected if pediatric dosages are revised as requested by the comments, the agency has published a separate document in the **Federal Register** that discusses pediatric dosages for OTC drug products. Therefore, comments regarding a weight-based, age-related pediatric dosage schedule for pseudoephedrine and other oral nasal decongestants are being deferred at this time and have been addressed in a separate notice entitled "Pediatric Dosing Information for OTC Human Drugs; Intent and Request for Information," published in the **Federal Register** on June 20, 1988 (53 FR 23180). Should pediatric dosage schedules, in general, be revised in the future, the final monograph for OTC nasal decongestant drug products will be amended accordingly.

E. Comments on Labeling of OTC Nasal Decongestant Drug Products

13. Two comments stated that FDA lacks statutory authority to prescribe exclusive lists of terms from which indications for use for OTC drug products must be drawn and to prohibit alternative labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer. One comment recommended that, instead of prohibiting the use of alternative truthful terminology, FDA should permit manufacturers to choose consumer oriented language to communicate the desired label indications, so long as such language is not false or misleading. Both comments noted that FDA had proposed certain revisions to the "Exclusivity Policy" on April 22, 1985 (50 FR 15810) and stated that they would be submitting further comments on that proposal.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either: (1) The specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "approved uses"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "approved uses"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "approved uses," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g).

In the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220 at 2238), supplemental language relating to indications had been proposed and captioned as "Other allowable indications." Under FDA's revised labeling policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful and nonmisleading language that would be allowed elsewhere in the labeling. In accordance with the revised labeling policy, such statements would not be included in a final monograph. However, the agency has decided that, because these additional terms have been reviewed by FDA, they should be incorporated, wherever possible, in final OTC drug monographs under the heading "Indications" as part of the indications developed under that monograph. (See comment 16 in section I.E. of this document.)

14. Four comments requested that § 341.80(b) of the tentative final monograph be amended to allow manufacturers to choose from among any of three basic indications provided, i.e., the common cold (cold), allergy, or sinusitis. The comments contended that the intended target populations for products promoted and marketed for treating the common cold, allergy, and sinusitis are different and that specific products should be allowed to be designed or positioned for specific consumer populations. One comment pointed out that the use of all three indications for all products containing oral nasal decongestants, as proposed in § 341.80(b), may not only be extraneous, but potentially confusing to consumers. Two comments provided examples of how this labeling could be extraneous: (1) Indications for hay fever or allergic rhinitis would be inappropriate on a product marketed as a "cold" product, and (2) indications for a cold would be inappropriate for persons suffering from allergy or sinusitis. One comment added that small packages of multi-ingredient combination products contain little label space for necessary indications and warnings. It is therefore important for the distributor of a product to have the option to eliminate indications which are not applicable to a particular segment of the market for which the product is positioned.

The comments requested, therefore, that the indications in § 341.80(b) be amended to allow manufacturers to choose from among any of the basic indications (i.e., the common cold (cold), allergy, or sinusitis) that are appropriate for the consumer market segment to which the product is directed. One comment suggested that § 341.80(b)(1) be modified to read as follows:

> The labeling of the product contains a statement of the indications under the heading "Indications" which includes one or more of the following indications: "For the temporary relief of nasal congestion due to" (select one of the following) "the common cold (cold)," "hay fever (allergic rhinitis)," or "associated with sinusitis."

The agency agrees with the comments that manufacturers should be allowed to choose from among any of the indications proposed for nasal decongestant drug products in § 341.80(b)(1) that are consistent with the intended use of the product.

Thus, in this final monograph the agency is revising the "Indications" in § 341.80(b)(1), to read as follows: (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in (i), (ii), and (iii) below):

(i) "due to" (select one of the following: "the common cold" or "a cold").

(ii) "due to" (select one of the following: "hay fever," "hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)").

(iii) "associated with sinusitis."

15. With regard to the indications proposed in § 341.80(b), two comments stated that the phrases "for the temporary relief of" and "temporarily relieves" are similar and should be interchangeable.

The agency agrees with the comments that the phrases are interchangeable. Therefore, the agency has included the option of using either phrase in the indications included in § 341.80(b) of this final monograph. (See comments 14 and 16 in section I.E. of this document.)

16. One comment requested that the "other allowable indications" proposed in § 341.80(b)(2) of the tentative final monograph be alternative statements rather than additional statements to the indications proposed in § 341.80(b)(1). The comment contended that this would permit meaningful alternate "consumer oriented" label indications. Another comment assumed that the "other allowable indications" proposed in § 341.80(b)(2) may be identified on product labels as "other indications" if they are separate from the indications identified in § 341.80(b)(1) and are not given greater prominence.

In this final monograph, the agency is revising the indications in § 341.80(b)(1) to allow manufacturers the option of using one or more of the indications (see comment 14 in section I.E. of this document.) The agency considers the required indication statement(s) essential in providing adequate and informative labeling to the consumer. Under the agency's revised labeling policy for OTC drug products, discussed in comment 13 in section I.E. of this document, the "other allowable indications" that were proposed in § 341.80(b)(2) of the tentative final monograph have been included in the final monograph as part of the indications in § 341.80(b). However, the agency does not consider the text of these "other allowable" indication statements as providing complete information that is comparable to the information contained in § 341.80(b)(1). Because they provide additional, complementary information, the previous "other allowable" indications are included in § 341.80(b)(2) of the final monograph as statements that may appear in the "APPROVED USES" boxed area in the labeling, in addition to one or more of the indications in § 341.80(b)(1).

Therefore, the labeling of the product may contain any (one or more) of the following statements, which appear in § 341.80(b)(2) of this final monograph, provided the required information identified in § 341.80(b)(1) (see comment 14 in section I.E. of this document) is also included:

(i) (Select one of the following: "For the temporary relief of" or "Temporarily relieves") (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Select one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; temporarily relieves sinus congestion and pressure."

(v) "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."

(See also comment 17 in section I.E. of this document.)

17. One comment requested modification of the "other allowable indications" for nasal decongestant drug products in proposed § 341.80(b)(2)(i) to include the terms "stuffed-up head" and "stuffy head" as follows: "For the temporary relief of (select one of the following): stuffy nose, stopped-up nose, nasal stuffiness, clogged-up nose, stuffed-up head, stuffy head."

The agency does not consider the terms "stuffed-up head" and "stuffy head" specific enough to be included in this final monograph. The agency believes that other terms could be used in the indication statements to provide more specific information to consumers about the action of this type of drug product than the comment's suggestion of the general terms "stuffed up head" and "stuffy head." In the tentative final monograph, the agency included "relieves sinus pressure" as a Category I indication for nasal decongestants (50 FR 2220 at 2231). Sinus pressure and sinus congestion are closely associated and if congestion is relieved, pressure also would be relieved (50 FR 2220 at 2232). Therefore, in this final monograph, the agency is including the term "sinus congestion" in the indications in § 341.80(b)(2)(iv) and (b)(2)(v). The agency concludes that the terms "sinus congestion" and "sinus pressure" provide more specific information than the comment's suggested terms. In addition, the agency is including these terms in § 341.80(b)(2)(iv) and (b)(2)(v) because those paragraphs primarily deal with "sinus" conditions, whereas the indication in § 341.80(b)(2)(i) primarily deals with "nose" conditions. (See comment 16 in section I.E. of this document for additional discussion of the other indications included in this final monograph.)

However, as discussed in comment 13 in section I.E. of this document, the agency has revised its labeling policy for OTC drug products. FDA has found that it simply is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs directly address only those labeling items that are related in a significant way to the safe and effective use of covered products by lay persons. These labeling items are the product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action. Truthful and nonmisleading terms that provide additional information about an OTC drug product but are not directly related to its safe and effective use are considered outside the scope of the OTC drug review and may appear elsewhere in the labeling,

separate from the monograph approved statements. Thus, because consumers are familiar with and use terms such as "stuffed-up head" and "stuffy head," the agency considers these terms as acceptable to be included elsewhere in the labeling (but such terms may not be intermixed with any portion of the labeling required by the monograph and may not detract from such required information). Terms outside the scope of the review will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act relating to labeling that is false or misleading.

18. One comment requested that the indication, "helps (select one of the following: relieve, alleviate, decrease, reduce) post-nasal drip" be added as an additional consumer claim for nasal decongestant drug products.

The Cough-Cold Panel placed a similar claim, "checking post-nasal drip," in Category III because such claims are unsubstantiated for nasal decongestants unless studies specifically designed to assess "post-nasal drip" are presented. The Cough-Cold Panel stated in 41 FR 38415 that studies of nasal decongestants have assessed the effect of nasal airway resistance or the ease of breathing but not the effect on rhinorrhea that causes post-nasal drip. The comment did not submit any data concerning the effect of nasal decongestants on rhinorrhea that would support a claim for "post-nasal drip."

Further, the agency is unaware of any data to support consumer recognition of an indication regarding post-nasal drip. The agency reviewed information submitted to the antihistamine final monograph rulemaking requesting an indication for "post- nasal drip." The comment asserted that substantial numbers of consumers recognize that relief of "post-nasal drip" is a desirable end benefit and that consumers clearly understand the term "post-nasal drip." The comment provided two consumer mail panel studies, which were designed to investigate consumer attitudes towards, and usage of, sinus and hay fever remedies. The comment stated that of the 263 responding sinus sufferers, 49 percent (129) considered relief of post-nasal drip important when choosing a sinus remedy. Similarly, 48 percent (119) of the 248 hay fever respondents indicated that relief of post nasal drip was important when choosing a hay fever product. The agency's review of the studies disclosed that they were not designed to demonstrate the effectiveness of OTC antihistamine drug products in relieving the symptom "post-nasal drip" or provide a basis for a "post-nasal drip" indication. These data, therefore, are not useful in supporting a "post-nasal drip" indication for nasal decongestant or antihistamine drug products.

Clinical studies specifically designed to demonstrate the effectiveness of nasal decongestants in relieving "post-nasal drip" would be necessary before this claim could be used in the labeling of any nasal decongestant drug product. Such studies should be designed to evaluate the symptom of "post-nasal drip" in terms of specific symptoms that can be recognized by consumers as "post-nasal drip." The agency suggests that any party interested in studying the use of a nasal decongestant for this claim meet with the agency to discuss an appropriate protocol before beginning the study. For the above reasons, indications pertaining to "post-nasal drip" are not being included in this final monograph for OTC nasal decongestant drug products.

19. Two comments stated that the agency should differentiate between "Warnings" and "Cautions" in OTC drug labeling, and one comment objected to the proposed elimination of the term "Caution(s)" in the labeling of OTC drug products. The comments contended that "Warnings" are harsher (stronger) and more serious than "Cautions" and even preclude use of a product under certain conditions. One comment stated that a "Caution," on the other hand, does not preclude use unless something occurs during use, but it often alerts the consumer to a potential problem. The comment added that a caution may also address a monitoring function to be performed while the product is in use. The second comment stated that a caution should be used to convey important information related to the safe and effective use of the product, but allow for judgment on the part of the user, e.g., "This product may cause drowsiness." The comment felt that the importance of the "Warnings" section was undermined if it contains too much information or if it includes less than serious language. The comment provided several examples of the differences between warnings and cautions and suggested that the agency also consider the term "precautions."

Section 502(f)(2) of the act 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. In addition, the term "precaution(s)," as in "Drug Interaction Precaution(s)" is often used in OTC drug monographs, but is listed under "Warnings" as, for example, in the rulemakings for OTC nasal decongestant drug products and OTC bronchodilator drug products. (See the Federal Register of January 15, 1985 (50 FR 2220 at 2239) and October 2, 1986 (51 FR 35326 at 35339), respectively.)

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 is not convinced that consumers will make the distinctions between "warnings" and "cautions" that the comments have made. Further, the agency does not believe that the importance of the "Warnings" section will be undermined if all of the information about unsafe use, side effects, and adverse reactions is presented under a single heading. 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, except in instances where the agency has stated that a particular warning statement must appear as the first warning after the "Warnings" heading, the agency has no objections if manufacturers list the various warnings statements in their order of preference, e.g., listing first those they consider more serious followed by those they consider to be less serious statements. Drug interaction precaution information will continue to be listed under the heading "Drug Interaction Precautions" as part of the warnings information.

20. One comment stated that it is difficult to read labels of nasal decongestant drug products because the containers are small and the print on the labels also is small. The comment was particularly concerned that the required warnings would not be legible and

recommended that the warnings should be "clearly, in sizable print, be evident, but only a minimum amount." The comment stated that it would be more useful if "warning sheets" or booklets were available with nasal decongestant packages. A second comment requested larger print size and more prominent location of warnings on nasal decongestant products.

In the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220), the agency simplified or revised several and deleted some of the warnings recommended by the Cough-Cold Panel. (See comments 13, 21, 24, 26, 28, and 29 in the tentative final monograph.) The agency believes that the labeling proposed in this final monograph includes only essential information that is necessary to assure proper and safe use of OTC nasal decongestant drug products by consumers. Moreover, the labeling of drugs must comply with section 502(c) of the act which states that a drug shall be deemed to be misbranded:

> If any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

In general, a product container label needs to bear the following information: A statement of ingredients (section 502(e) of the act), name and address of the manufacturer, repacker, or distributor (section 502(b)(1) of the act), a net contents statement (section 502(b)(2) of the act), a lot number (21 CFR 201.18), and an expiration date (21 CFR 201.17). In some situations, other labeling information is required to appear on the immediate container labeling, e.g., the Reye syndrome warning for drug products containing salicylates (21 CFR 201.314).

When an OTC drug product is packaged in a container that is too small to contain all the required labeling, the agency recommends that the product be enclosed in a carton or be accompanied by a package insert or booklet that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label. Manufacturers who use supplemental labeling should be able to readily provide all labeling information in a larger print size than if all of the labeling is presented on the immediate container. Further, the agency is aware that many manufacturers use bold lettering and a colored label to emphasize certain labeling information, including warnings, on the immediate container and in package inserts. All manufacturers are encouraged to use these as appropriate to highlight and emphasize certain labeling information for the consumers. The agency previously published a request for public comment (56 FR 9363 to 9365, March 6, 1991) on the issue of print size and style of labeling for OTC drug products, and will evaluate comments received before making a final decision on the feasibility of establishing a Federal regulation pertaining to print size and style of OTC labeling.

The Nonprescription Drug Manufacturers Association (NDMA) has recently promulgated guidelines for industry to consider when examining product labels for readability and legibility (Ref. 1). These guidelines are designed to assist manufacturers in making the labels of OTC drug products as legible as possible. The agency commends this voluntary effort and urges all OTC drug manufacturers to examine their product labels for legibility.

Reference

(1) "Label Readability Guidelines," The Nonprescription Drug Manufacturers Association, Washington, copy included in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

21. Two comments pointed out that the warning for oral nasal decongestants in proposed § 341.80(c)(1)(i)(*b*) (which states: "Do not take this product for more than 7 days. If symptoms do not improve or are accompanied by fever, consult a doctor.") and a similar warning for children in § 341.80(c)(1)(ii)(*b*), could be read to warn against the use of Category I OTC oral nasal decongestant drug products without first consulting a doctor if a fever is present initially. The comments stated that in the advance notice of proposed rulemaking for OTC internal analgesic-antipyretic drug products, the Internal Analgesic Panel classified as Category I the combinations of one or two Category I analgesic-antipyretic active ingredients "* * * with generally recognized as safe and effective nasal decongestant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, * * * for the reduction of fever, * * * " (42 FR 35370, July 8, 1977). One comment contended that while the proposed warning may have limited significance for single ingredient nasal decongestant drug products, it would have a serious and unwarranted adverse effect on the use of combination drug products containing a nasal decongestant along with an analgesic-antipyretic. The comment urged that the proposed warning be reworded to explicitly permit use of a combination product containing an oral nasal decongestant and an antipyretic agent(s) when concurrent symptoms of nasal congestion and fever are present.

The second comment stated that billions of doses of oral nasal decongestants have been used OTC for many years without such a label warning. The comment added that it was unaware of any safety problems that have occurred as a direct consequence of a consumer using a nasal decongestant in the presence of minor fever of short duration, which is the case in the vast majority of instances in which fever is present. On the other hand, the comment contended, the presence of high fever is of importance to the well-being of the consumer, and a doctor should be consulted if such occurs. The comment requested that the above-referenced warnings be amended to read: "(*b*) If symptoms do not improve in 7 days or are accompanied by high fever, consult a doctor."

The comment also stated that some allergic episodes (and even colds) occasionally continue for more than 7 days, particularly in humid climates or in periods of high pollen counts. Therefore, an absolute 7-day use limitation may not always be appropriate. Moreover, the comment stated that its amended warning would be equally informative to consumers who may be taking an oral nasal decongestant product without an antipyretic ingredient as well as to those who may take a combination which includes antipyretic ingredient(s). Thus, the comment requested that this amended warning be included in the following final monographs: (1) OTC nasal decongestant drug products; (2) OTC internal analgesic-antipyretic drug products; and (3) OTC cough-cold combination drug products.

The Cough-Cold Panel noted that a slight fever may be present with the common cold (41 FR 38312 at 38321). The Internal Analgesic Panel stated that antipyretics (fever reducers) may be safely used for self-medication when fever is due to the common cold or flu (42 FR 35346 at 35351). The warnings in § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) are not meant to restrict use of an oral nasal decongestant in the presence of minor

fever of short duration such as that which might be associated with a common cold. The agency agrees that a nasal decongestant can be used in such situations. The intent of the warnings is to alert consumers that the presence of a fever might indicate a more serious condition, such as a secondary bacterial infection, for which a doctor should be consulted. For example, a nasal obstruction accompanying a common cold can result in a middle ear infection (acute otitis media). Usually, the first complaint of a middle ear infection is a persistent, severe earache. Other symptoms, such as fever, nausea, vomiting, and diarrhea may occur in young children (Ref. 1). Pneumonia is also often preceded by an upper respiratory infection. Symptoms include chills, sharp pain in the chest, cough, fever, and headache (Ref. 2). Thus, because the agency believes that it is important for consumers to recognize that all fevers are not insignificant occurrences, the word "fever" as proposed in the tentative final monograph is being retained in this final monograph.

This warning for oral nasal decongestant drug products is consistent with the warning included in the final monographs for single ingredient antitussive drug products and single ingredient expectorant drug products, which states: "* * * If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor." (See §§ 341.74(c)(1) and 341.78(c)(2)). These warnings are not meant to restrict the use of an antitussive or an expectorant in the presence of minor fever of short duration such as that which might be associated with a common cold. However, as with the warning for nasal decongestants, the intent of the warnings is to alert consumers that the presence of a fever might indicate a more serious condition, and a doctor should be consulted.

The agency has previously considered inclusion of the word "high" (in reference to fever) in this warning in the final monograph for OTC antitussive drug products. (See 52 FR 30042 at 30054, August 12, 1987.) In that proceeding, the agency determined that the word "high" would not be included in the warning because it is important for the consumer to recognize the presence of fever regardless of whether the fever is high or low. The agency concludes that this principle is equally applicable to the labeling of OTC nasal decongestant drug products. Therefore, the agency is not adopting the second comment's suggested wording related to the use of the term "high" to describe fever.

The agency agrees with the comment that an absolute 7-day limitation may not always be appropriate for oral nasal decongestant drug products. Further, the final monographs for OTC antitussive and expectorant drug products (21 CFR part 341) do not impose a 7-day use limitation, and the agency concludes that such a limitation is also not necessary for oral nasal decongestant drug products. Therefore, the warnings proposed in § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) in the tentative final monograph are revised as follows: "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor." These warnings appear in § 341.80(c)(1)(i)(B) and (c)(1)(ii)(B) of this final monograph.

With regard to labeling of cough-cold combination drug products for which the labeling in the individual applicable monographs conflicts or is inappropriate, the agency has proposed specific labeling in § 341.85 of the tentative final monograph for OTC cough-cold combination drug products. (See 53 FR 30522 at 30562 to 30564.) The antipyretic ingredient in an oral nasal decongestant-analgesic-antipyretic combination drug product would be used specifically to treat a fever. Normally, the labeling for such a product would contain the appropriate portions of the monograph labeling for nasal decongestant and analgesic-antipyretic ingredients. However, the agency recognized that the warnings for nasal decongestants proposed in § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) of the tentative final monograph would be inconsistent with the presence of the analgesic-antipyretic ingredient(s) in the product. Therefore, to eliminate this inconsistency, the agency proposed the following warning for such products labeled for use by adults in the cough-cold combinations tentative final monograph: "Do not take this product for more than 10 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor." For products labeled for use by children 2 to under 12 years of age, the proposed warning reads as follows: "Do not give this product to children for more than 5 days. If symptoms do not improve or are accompanied by fever that lasts for more than 3 days, or if new symptoms occur, consult a doctor." (See 53 FR 30522 at 30563.) The agency will address this warning in the final monograph for OTC cough-cold combination drug products, in a future issue of the Federal Register.

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(1) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, pp. 2331–2332, 1992.

(2) Berkow, R., editor, "The Merck Manual," 16th ed., Merck and Co., Rahway, NJ, pp. 681–685, 1992.

22. One comment contended that the agency's proposed drug interaction precautions for adults and children in § 341.80(c)(1)(i)(*d*) and § 341.80(c)(1)(ii)(*d*), respectively, essentially duplicate statements required in other warnings. The comment requested that the proposed warning in § 341.80(c)(1)(i)(*c*) be modified to include the "Drug Interaction Precaution" information in § 341.80(c)(1)(i)(*d*) to read as follows: "Do not take this product if you are being treated for heart disease, depression, high blood pressure, thyroid disease, diabetes, or have difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." Likewise, the comment requested that the proposed warning in § 341.80(c)(1)(ii)(*c*) be modified to include the "Drug Interaction Precaution" information in § 341.80(c)(1)(ii)(*d*) to read: "Do not give this product to children who are being treated for heart disease, thyroid disease, diabetes, high blood pressure, or depression unless directed by a doctor." The comment concluded that these revisions would eliminate redundancy in the warnings language.

The agency agrees that the statements are similar but does not agree that drug interaction precautions should be combined with warnings. The agency believes the drug interaction precaution needs to be highlighted in order to adequately inform individuals who may not otherwise be aware of serious (even life-threatening) adverse effects due to potentiation of the adverse effects of one drug by another taken concurrently.

In discussing drug interactions, the Cough-Cold Panel stated that it had recommended appropriate labeling for drug interactions where there are serious concerns (41 FR 38312 at 38335). In the case of nasal decongestants, the Cough-Cold Panel stated that patients taking other drugs (e.g., monoamine oxidase inhibitors whose action can intensify sympathomimetic drug action), should not use oral nasal decongestants except under the advice and supervision of a physician (41 FR 38312 at 38397). The Cough-Cold Panel therefore recommended a specific warning, in the form of a drug interaction precaution, to alert the subgroup of the OTC nasal decongestant target population taking prescription medication for certain

chronic disease conditions, to their special risk in using OTC nasal decongestants concurrently. The Cough-Cold Panel recommended the following drug interaction precaution statement: "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician." (See 41 FR 38312 at 38423.) For these reasons, the agency also proposed this drug interaction warning for OTC sympathomimetic amine bronchodilator drugs (41 FR 38312 at 38370 through 38373).

The agency discussed this statement in the tentative final monograph for OTC nasal decongestant drug products (50 FR 2220, January 15, 1985). In response to the Cough-Cold Panel's recommendation, two comments contended that terms such as "antihypertensive," "antidepressant," and "monoamine oxidase inhibitor" (MAOI) are highly technical; that only a small percentage of the population is likely to understand this warning; and that including such a warning in the labeling of an OTC drug is contrary to the well-established principle that unnecessary or confusing precautions tend to dilute the significance of all instructions in the labeling and, hence, should be avoided (50 FR 2220 at 2231). Accordingly, the agency proposed to simplify the precaution statement as follows: "*Drug interaction precaution.* Do not take this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." (See proposed § 341.80(c)(1)(i)(*d*).) Also with the tentative final monograph, the agency proposed to add new § 341.80(c)(1)(ii)(*d*) for children, as follows: "*Drug Interaction Precaution:* Do not give this product to a child who is taking a prescription drug for high blood pressure or depression, without first consulting the child's doctor." The wording for OTC bronchodilator drug products was similarly revised in the tentative final monograph (47 FR 47520 at 47523) and the final monograph (51 FR 35326 at 35338).

After publication of the tentative final monograph for OTC nasal decongestant drug products, the agency became aware of a need to modify the wording of the drug interaction precaution statement. Information was submitted to the agency showing that the antitussive ingredient dextromethorphan interacts with prescription drugs containing MAOI's. Case reports and articles in the literature describe severe reactions, including death, from this combination of drugs. In preparing a proposal to amend the final monograph for OTC antitussive drug products to provide for a new drug interaction precaution for that class of OTC drugs, the agency determined a need to modify the language of the existing precaution statement for OTC bronchodilator and nasal decongestant drugs, largely because of expanded use of MAOI drugs. There is evidence that MAOI drugs are also being used to treat conditions, such as bulimia and panic disorder, that are not readily associated with depression. Further, the newer MAO B inhibitors are being used to treat Parkinson's disease. Finally, the use of MAOI's in hypertension has essentially ceased. In order to have consistent language among the three drug classes, the agency published proposals to amend the antitussive final monograph (57 FR 27666), bronchodilator final monograph (57 FR 27662), and the nasal decongestant tentative final monograph (57 FR 27658) to provide for the following warning:

Drug interaction precaution. Do not use this product if you are taking a prescription drug containing a monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), without first consulting your doctor. If you are uncertain whether your prescription drug contains an MAOI, consult your doctor before taking this product.

The case reports and literature articles are discussed in detail in the proposed amendment to the final monograph for OTC antitussive drug products (57 FR 27666).

The comments received in response to the proposed amendments are discussed in detail in a final rule for OTC antitussive drug products (58 FR 54232, October 20, 1993) and OTC bronchodilator drug products (58 FR 54238, October 20, 1993). In brief, four comments that suggested modifications to the wording of the drug interaction precaution statement were not adopted, and one comment that suggested a 2-week washout period be included was adopted.

Accordingly, the agency is amending § 341.80(c)(1)(i)(*d*) for OTC nasal decongestant drug products to read:

Drug interaction precaution. Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

Also, the agency is amending § 341.80(c)(1)(ii)(*d*) to read:

Drug interaction precaution. Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product.

23. Three comments contended that the agency should not require the warning for topical nasal decongestants proposed in § 341.80(c)(2)(iii)(*b*) of the tentative final monograph, which reads: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

One comment contended that the warning should not be required because systemic distribution of topical nasal decongestants is minimal. A second comment stated that such a warning is not warranted for topical products containing oxymetazoline. Referring to studies in dogs that compared the doses of oxymetazoline given intranasally and intravenously to elicit a cardiovascular effect (i.e., increase in blood pressure) and that showed substantial differences, the comment indicated that the amount of oxymetazoline required to elicit any systemic effect by the intranasal route would be virtually unachievable with marketed products. Based on the amount of the drug which is required to cause a systemic effect, the comment argued that there is no reason to believe that patients with cardiac problems, diabetes, or hyperthyroidism would be at any greater risk than the general population. In addition, the comment stated that its review of adverse experience files showed no cardiovascular side effect from oxymetazoline that was not associated with significant overuse, either in frequency of use, quantity of use, or both. The comment stated that the agency's proposed warning not to overuse the product deals adequately with risks to patients with cardiac problems, diabetes, or hyperthyroidism and that the additional warning is unnecessary.

The third comment indicated that the proposed warning should be deleted from the monograph because it is conjectural that systemic effects can occur as a result of absorption from the gastrointestinal tract if an excessive amount of topically applied nasal decongestant drug is swallowed. The comment stated that it was unaware of any data that support the position that an excessive amount of drug can be, or

is, swallowed when the product is used as directed. The comment cited numerous studies to support its position (Refs. 1 through 19). In addition, the comment attached a summary of published studies addressing the issue of intranasally-applied decongestants and possible cardiovascular changes (Ref. 20). The summary indicated that oral threshold doses reported to be associated with changes in pulse rate and/or blood pressure are 6 to 10 times higher than the maximal dose of phenylephrine or ephedrine administered intranasally. In the case of phenylephrine hydrochloride, the comment stated that if an entire dose of a 0.5-percent nasal spray, which contains 1.5 mg phenylephrine hydrochloride, were ingested, it would amount to only a small fraction of the Category I recommended oral dose of 10 mg for this drug. In the case of 0.5 percent ephedrine sulfate, a typical adult dose of 0.6 mg would be delivered and, 100 percent of the dose, if ingested, would amount to only a small fraction of the Cough-Cold Panel's recommended oral dose of 8 to 12 mg as a bronchodilator (41 FR 38312 at 38408).

The agency has reviewed the studies cited by one comment as well as other pertinent information concerning the side effects caused by topical nasal decongestants. Based on its review of the available data and information, the agency concludes that the warning—concerning the use of topical nasal decongestants in patients with heart disease, high blood pressure, thyroid disease, and diabetes—as discussed in the tentative final monograph (50 FR 2220 at 2222 to 2223) is appropriate for topical nasal decongestant drug products containing ephedrine or one of its salts, phenylephrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, and xylometazoline hydrochloride. The agency does not believe that the studies adequately support the safe use of topical nasal decongestants in patients with heart disease, high blood pressure, thyroid disease, or diabetes without the supervision of a physician. Further, the agency's adverse reaction data indicate that, after rebound congestion, cardiovascular effects are among the most numerous adverse effects reported.

The agency has reviewed its adverse reaction report files (Ref. 21) and finds that cardiovascular effects such as bradycardia, tachycardia, hypertension, and hypotension have been reported for products containing topical nasal decongestants, particularly for oxymetazoline. In most of the cases of cardiovascular effects, the topical nasal decongestant drug was reported to be the only drug used by the patient and was believed to be the suspect drug. Based on these adverse reaction files, the agency is concerned that certain individuals may be more susceptible to developing cardiovascular effects when using topical nasal decongestants. Further, although topical nasal decongestant drugs are recommended for no more than 3 days use, the agency is aware that excessive use of topical nasal decongestants does occur (see comment 2 in section I.A. of this document). Such excessive use could also increase the possibility that individuals with the conditions listed in the warning might develop adverse effects.

The agency does not believe that the studies submitted by one of the comments adequately support the safe use of topical nasal decongestants containing ephedrine or one of its salts, phenylephrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, or xylometazoline hydrochloride in patients with heart disease, high blood pressure, thyroid disease, or diabetes without the supervision of a physician. A number of the studies (Refs. 1 through 8) were not useful to evaluate topical effects of the nasal decongestants because the drugs were administered by oral or injectable routes. In 11 of the submitted studies (Refs. 9 through 19), nasal decongestants were administered intranasally in subjects with cardiovascular disorders, diabetes, or thyroid disease. In 1 of the 11 studies (Ref. 19), the number of hypertensive subjects could not be determined. In the remaining 10 studies, 833 subjects were studied but only 50 subjects had the conditions referred to in the warning. Thus, the agency does not consider this limited number of subjects adequate to support deletion of the warning.

The data also show that the oral doses of some topical nasal decongestants that are required to produce adverse reactions exceed the recommended topical dosages; however, none of the submitted data address the extent of absorption of nasal decongestants from the nasal mucosa, and this may be more analogous to intravenous administration than to oral administration of the drug. Many drugs (e.g., sublingual nitroglycerin, nitroglycerin spray, corticosteroids) are absorbed well from the mucosa of the oropharynx and can be more rapidly and completely absorbed than when ingested orally.

Further, the submitted data do not contain sufficient information to exclude the systemic effects alluded to in the warning. Actual data on blood pressure changes were not provided in most of the studies, and the degree of absorption of the drugs from topical intranasal administration was not addressed. Although topical nasal decongestants are administered in smaller doses than the oral doses of these drugs, the safety of these drugs when used without physician supervision by patients with heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland has not been adequately demonstrated.

Based on the above reasons, the agency is retaining the following warning for topical nasal decongestant products containing ephedrine, phenylephrine hydrochloride, naphazoline hydrochloride, oxymetazoline hydrochloride, or xylometazoline hydrochloride that was proposed in the tentative final monograph: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

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(19) Hagen, W.J., and M.G. Trelles, "A New Local Decongestant of Unusually Low Toxicity," *The Eye, Ear, Nose, and Throat Monthly*, 39:56–57, 1960.

(20) "Summary of Published Evidence Relating to the Issue of Intranasally-Applied Decongestants and Possible Cardiovascular Changes," The Proprietary Association, Washington, Appendix A of Comment No. C206, Docket No. 76N–052N, Dockets Management Branch.

(21) Department of Health and Human Services, Food and Drug Administration, "Spontaneous Reporting System, Line Listing of Adverse Reports: Nasal–76–93," 1976–1993, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

24. One comment contended that the proposed warnings in § 341.80 for topical nasal decongestant sprays and drops (which state: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor;" "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur;" and "Do not use this product for more than 3 days. If symptoms persist, consult a doctor.") do not apply to its company's "innovative and unique one-way metered pump spray delivery system." The comment explained that the metered delivery system for its topical nasal decongestant drug products substantially reduces dosage variability, assures uniform dosage and spray pattern, and thereby further minimizes any possibility of significant systemic absorption and systemic side effects. For this reason, the comment recommended that for these products the agency eliminate the warning in proposed § 341.80(c)(2)(iii)(*b*) not to use topical nasal decongestants if certain disease conditions are present. Stating that the spray pattern achieved with the pump virtually eliminates the nasal irritation and rebound congestion sometimes associated with conventional sprays and drops and that marketing experience has confirmed the purpose of the pump's design, the comment also contended that the warnings proposed in § 341.80(c)(2)(i)(*a*) and (c)(2)(iii)(*a*) concerning burning, stinging, etc., and a restriction to only 3 days' dosage should not be required for its metered pump products.

The comment did not submit any data to support its contention that the use of a metered pump delivery system makes the above mentioned warnings unnecessary. Furthermore, the agency believes that regardless of the uniformity of the dosage and spray pattern of a topical nasal decongestant, the pharmacologic action of nasal decongestant active ingredients can produce adverse reactions in some susceptible individuals who have heart disease, high blood pressure, diabetes, etc. Thus, in the interest of consumer safety, the warning proposed in § 341.80(c)(2)(iii)(*b*) would still be applicable, regardless of the nasal spray delivery system. Also, a uniform dosage and spray pattern would not eliminate the possibility of overuse of the topical nasal decongestant drug product. An individual might use too much of the spray by repeatedly applying the medication or by using the product longer than the recommended 3 days use. Thus, rebound congestion could occur and the warning in § 341.80(c)(2)(iii)(*a*) would be applicable. The agency is unaware of data to support the comment's contention that a uniform dosage and spray pattern could help to lessen adverse effects such as burning, stinging, sneezing, etc., which might be caused by an excessive dose of a topical nasal decongestant. In the absence of data, the agency cannot agree with the comment that the warning regarding burning, stinging, sneezing in § 341.80(c)(2)(i)(*a*) (redesignated as § 341.80(c)(2)(i)(B) in this final monograph) is unnecessary for its pump spray delivery system. Therefore, the agency concludes that the warnings for topical nasal decongestants mentioned by the comment are applicable regardless of the spray delivery system.

The agency notes that a request of the type submitted by the comment (for deletion of certain warnings for a specific metered pump delivery system) could be considered as a request for an exemption from the monograph requirements or as a request for a monograph deviation. For an exemption, which would require the submission of a petition to amend the final monograph, data would have to be submitted to support the comment's contention that certain warnings are unnecessary for the metered pump spray delivery system. An exemption from these warning statements could then be included in the monograph for all nasal decongestant ingredients marketed in the specified metered dose spray dosage form along with the specifications for the specific metered pump spray delivery system. The agency believes that it would be difficult to write such specifications for inclusion in a monograph and thus considers a monograph deviation to be a more suitable alternative. A monograph deviation is covered by the regulations in 21 CFR 330.11. These regulations provide for the submission of a limited new drug application (NDA) covering only the deviation from the final monograph. Under these regulations, data submitted in support of an NDA for a product that deviates from an OTC drug final monograph must be in the form required by 21 CFR 314.50. Also, the request must include a statement that the product meets all conditions of the applicable OTC drug monograph except for the deviation for which approval is requested. The application may omit all information except that pertinent to the deviation. For the particular product discussed in the comment, the manufacturer should provide sufficient manufacturing control data to assure FDA of the uniformity of the metered dose delivery and of the spray pattern claimed for the drug product, and should include adequate clinical data to confirm that the warnings are unnecessary.

25. One comment recommended that the following statements be allowed for topical nasal decongestants marketed in a one-way metered pump delivery system: "Won't draw back nasal fluids," "unique one-way pump prevents draw-back contamination," "protects against

draw-back contamination," and "unique metered spray delivers a controlled/metered dose." In addition, the comment contended that "accurate" statements such as "long lasting relief" are appropriate for oxymetazoline-containing nasal decongestant drug products.

The agency believes that information describing a metered dose delivery system, such as that recommended by the comment, is product specific and above and beyond the scope of the standards set by this final monograph for OTC nasal decongestant drug products.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions determined during the review are allowable ingredients and the allowable labeling for those ingredients. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of drug products by consumers. OTC drug monographs establish the allowable labeling for the following: the product statement of identity; the names of active ingredients; the indications for use; the directions for use; the warnings against unsafe use, side effects, and adverse reactions; and the claims concerning the mechanism of drug action. Accordingly, such information as that recommended by the comment is outside the scope of the OTC drug review.

The agency emphasizes that even though such information is outside the scope of the OTC drug review, it may be used in labeling subject to the prohibitions in section 502 of the act relating to labeling that is false or misleading. Such information will be evaluated by the agency on a case by case basis in conjunction with normal enforcement activities relating to that section of the act. Moreover, any information that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

Regarding the comment's claim of "long lasting relief" for oxymetazoline-containing nasal decongestant drug products, the agency notes that oxymetazoline hydrochloride has a frequency of use of "not more often than every 10 to 12 hours" which is the longest duration of action of any topical nasal decongestant in the monograph. As stated in the tentative final monograph for OTC nasal decongestant drug products, the "duration of effect has been included in the established dosages and directions for these products by stating the frequency of use (in terms of hours), which indirectly tells the consumer the duration of the products' effects" (50 FR 2220 at 2236). Although not included in the monograph, the agency has no objection to a statement such as "long lasting relief" appearing in the labeling of an OTC nasal decongestant drug product containing oxymetazoline hydrochloride. However, as stated above, such statements are subject to the prohibitions in section 502 of the act and may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

26. Two comments suggested that the proposed warning for oral nasal decongestants in § 341.80(c)(1)(i)(*a*) and (c)(1)(ii)(*a*) (which states: "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur.") be revised. One comment suggested revising the warning sections to state: "Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a physician." This comment stated that, as the warning presently reads, it might suggest to consumers that nervousness, dizziness, and sleeplessness are the only consequences of exceeding the recommended dose, which is not necessarily so. The comment added that "nervousness, dizziness, and sleeplessness are significant enough to be a separate warning as they may, on occasion, occur at the recommended dose." The second comment suggested that the warning sections be rewritten to state: "Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, consult a doctor." The comment explained that a patient's medical history information is needed before a doctor can appropriately advise the patient whether to continue the same dose, decrease the dose, or discontinue the drug if the above-mentioned symptoms occur.

The agency agrees with the comments that the warnings for oral nasal decongestants proposed in § 341.80(c)(1)(i)(*a*) and (c)(1)(ii)(*a*) of the tentative final monograph could be revised to make them separate statements. Both comments proposed the same first statement, which is the same language as proposed in the tentative final monograph and which the agency is adopting in this final monograph. However, the comments differ in their suggested second statement. The second comment did not state to discontinue use of the drug if the above-mentioned symptoms occur. The agency believes that if nervousness, dizziness, or sleeplessness occur with use of a nasal decongestant drug, it is best to advise the consumer to discontinue use of the drug as a safety measure, and to consult a doctor for advice. In addition, in order to emphasize that the drug should not be overused, the agency is requiring that the first part of the warning appear on the label of the product in boldface type. Therefore, in the final monograph, the warnings read as follows: "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

27. One comment contended that the proposed warning for topical nasal decongestants in § 341.80(c)(2)(i)(*a*) (which states: "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur.") does not appear to be justified on the basis of consumer information and should be deleted from the monograph. The comment stated that one major firm reviewed its consumer complaint file on nasal sprays over a period of 5 years and found an average complaint rate of less than one complaint per million packages sold. The comment added that other firms have reported similar data. The comment questioned the logic of the cause and effect statement contained in the warning as it applies to topical nasal decongestant sprays and drops, i.e., that the reactions of "burning, stinging, sneezing, or increase of nasal discharge" will be the result of exceeding the recommended dosage. The comment argued that even if an excessive amount of spray or drops is used, which seems highly unlikely, the solution will either run out of the nose or drain to the back of the throat or both. In either case, the comment indicated that the amount of liquid that will adhere to the nasal mucosa is relatively constant.

In the tentative final monograph for OTC nasal decongestant drug products, the agency reviewed a related comment regarding the warning "Do not exceed recommended dosage because burning, stinging, sneezing, or increase of nasal discharge may occur." The agency concluded that this warning statement should apply to all topical nasal decongestant active ingredients administered as a drop, spray, jelly, or in an inhalant dosage form. (See 50 FR 2220 at 2232 to 2233.)

The agency also reviewed the labeling of topical nasal decongestant drug products previously approved under NDA's. The NDA labeling for products containing the nasal decongestant active ingredient oxymetazoline contained the statement: "Local stinging and slight burning can occur with any topical nasal decongestant" (Ref. 1). The NDA labeling for a product containing xylometazoline hydrochloride contained the following statement in the "Adverse Reactions" section: "Because of the pharmacological relationship among sympathomimetic nasal decongestants, the following types of effects may occur: burning, stinging, dryness of the nasal mucosa, sneezing; * * *." (Ref. 2). Furthermore, the AMA "Drug Evaluations Annual" describes typical adverse reactions of topical nasal decongestants as temporary discomfort such as stinging, burning, or dryness of the nasal mucosa, while the specific adverse reactions for naphazoline, oxymetazoline, and xylometazoline include sneezing as well (Ref. 3). Thus, the agency concludes that a warning concerning burning, stinging, sneezing, or an increase in nasal discharge is supported by clinical evidence and that the consumer complaint data, as presented by the comment, are inadequate to substantiate deletion of such a warning from the monograph. Based on the NDA labeling and AMA "Drug Evaluations," the agency believes that burning, stinging, sneezing, or an increase in nasal discharge may occur at recommended dosages and has revised the warning into two separate warnings to clarify that these side effects can occur at recommended doses. Therefore, the following revised warnings are being included in the final monograph: "Do not exceed recommended dosage," and "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge." Additionally, in order to emphasize that the drug should not be overused, the agency is requiring that the warning "Do not exceed recommended dosage" appear on the label of the product in boldface type.

References

(1) Copy of FDA approved labeling from NDA 14–717, in OTC Vol. 04NFM, Docket No. 76N–052N, Dockets Management Branch.

(2) Copy of FDA approved labeling from NDA 11–919 in OTC Vol. 04NTFM, Docket No. 76N–052N, Dockets Management Branch.

(3) "Drug Evaluations Annual," American Medical Association, Milwaukee, WI, p. 408 and pp. 415–418, 1991.

28. One comment disagreed with the agency's proposed warning for topical nasal decongestant drug products containing 1 percent phenylephrine hydrochloride, which states: "Frequent use of this product may cause nasal congestion to recur or worsen." The comment contended that the data in the two clinical studies (comparing the safety and effectiveness of phenylephrine 1 percent vs. phenylephrine 0.5 percent) that were reviewed by the agency in the tentative final monograph (50 FR 2220 at 2229) were insufficient to warrant the proposed warning. The comment argued that the agency itself admits that "* * * the differences in side effects between the two groups [0.5 percent vs. 1 percent phenylephrine] were not statistically significant" (50 FR 2229). The comment stated that one of the studies, by Jolly et al. (Ref. 1), confirms this view by noting that "The higher incidence of responses which probably reflects rebound hyperemia in the 1-percent group (19 percent) as compared to the 0.5-percent group (4 percent) is of questionable significance from the statistical standpoint." The comment added that Jolly et al. question the reliability of the method used in the study for assessing side effects. In addition, the comment contended that even if one were to assume that the method of data collection on side effects used by Jolly et al. was unquestionable, the two studies are not confirmatory in relation to the "possible" effect seen in the Jolly et al. study. The comment also mentioned that critical information (i.e., the use of prestudy medication and the baseline conditions of individuals who were reported to have experienced the side effect of congestion during drug usage periods) is missing from the assessment of side effects in these studies.

In summary, the comment stated that the two clinical studies were designed to assess efficacy, and the methodology was not sufficiently sensitive to define confidently a comparative safety profile for the two concentrations (0.5 and 1 percent) of phenylephrine. The comment concluded that because the suggestive data form at best a possible link of a side effect and are insufficient to warrant a label warning for products containing 1 percent phenylephrine, the proposed warning should not be included in the final monograph.

The agency disagrees with the comment that the two clinical studies were designed to assess only effectiveness. Information in the manufacturer's comment shows that the two clinical studies were conducted to assess "* * * the relative safety of the two concentrations," and "* * * to compare the tolerance exhibited * * * to [0.5 and 1 percent phenylephrine hydrochloride nose drops) under conditions of exaggerated (i.e., maximum limit of the present recommended dosage) use" (Ref. 2). In reviewing the Jolly et al. study (Ref. 1), the agency observed that:

> Twelve subjects who received the 1-percent concentration and 10 who received the 0.5-percent concentration experienced side effects such as headache, nausea, dizziness, nasal edema, and erythema. The differences in side effects between the two groups were not statistically significant. However, FDA notes that the data did suggest that the 1-percent concentration seemed more likely to induce rebound congestion. The investigator also noted that the 0.5-percent concentration may be slightly better tolerated (Ref. 3).

As discussed by the Cough-Cold Panel in its report, topical nasal decongestants are known to cause rebound congestion with continued frequent use (41 FR 38312 at 38396 to 38403). However, the Cough-Cold Panel felt that the problem could be minimized if topical nasal decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days (41 FR 38396). Rebound congestion occurs when topical nasal decongestants (i.e., nasal sprays, drops, jellies, and some inhalants) are used too often and for too long a period of time. Prolonged and continued use of topical nasal decongestants causes the nasal mucous membranes to become more congested and swollen as the effect of the drug wears off. The recurrence of congestion causes the user to reapply the drug. Repeated applications of the drug cause the nasal passages to reopen, but only briefly. This effect leads to continued use of the drug and perpetuates the rebound phenomenon. As discussed in comment 2, the agency has concluded that the 3-day use warning does not adequately explain to consumers the problem of rebound congestion. Therefore, the agency is clarifying the 3-day use warning as follows: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." These same revisions are being made in the 7-day use warning for l-desoxyephedrine that appears in § 341.80(c)(2)(ii) of this final monograph.

Based on the above discussion, the agency is deleting the specific warning for 1 percent phenylephrine hydrochloride that was proposed in the tentative final monograph in § 341.80(c)(2)(v) and is instead requiring that 1 percent phenylephrine hydrochloride, as well as all other

topical nasal decongestants except l-desoxyephedrine, bear the warning "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." This warning appears in §§ 341.80 (c)(2)(iii)(A), (c)(2)(v), (c)(2)(viii), and (c)(2)(ix) of this final monograph.

The agency's detailed comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) Jolly, E. R. et al., "Comparative Determination of Two Formulations of Neosynephrine," draft of unpublished study, Comment No. C0125, Docket No. 76N–0052, Dockets Management Branch.

(2) Comment No. C0125, Docket No. 76N–0052, Dockets Management Branch.

(3) Letter from W. E. Gilbertson, FDA, to E. J. Hiross, Sterling Drug, Inc., coded LET081, Docket No. 76N–052N, Dockets Management Branch.

29. One comment stated that, to its knowledge, no studies exist which show a definite association between the use of propylhexedrine and the occurrence of rebound congestion. The comment stated that one 2-week study and a single-dose study cited by the Cough-Cold Panel show that rebound congestion is not a problem with propylhexedrine, and a third study was ambiguous and results only "suggest a possible rebound congestion" (41 FR 38312 at 38402). The comment added that there are no studies which conclude that 3 days is the duration of therapy which reduces any risk of rebound congestion, and contended that the agency's proposed 3-day use limitation warning in § 341.80(c)(2)(vi) and (c)(2)(x) is arbitrary and unsubstantiated. The comment recommended that the agency revise proposed § 341.80(c)(2)(vi) and (c)(2)(x) to read: "Not to be used for prolonged periods."

The agency has reevaluated the studies cited by the comment (Refs. 1, 2, and 3). One study by Connell (Ref. 1) involved 64 adults with nasal congestion associated with acute coryza. The study was designed to compare the effect of a propylhexedrine inhaler on nasal airway resistance measured before inhalation to develop baseline data and after inhalation to measure the response pattern. With respect to this study, the Cough-Cold Panel stated that "measurements made 4 hours after the initial inhalation, that is, 2 hours after the repeat inhalation, suggest a possible rebound congestion" (41 FR 38312 at 38402). In a single-dose study by Hamilton (Ref. 2), the nasal decongestant effect of a propylhexedrine inhaler was compared with a placebo inhaler in 50 adult subjects with nasal congestion due to head cold. The subjects were divided equally between active and placebo groups. This study concluded that drug action of the propylhexedrine inhaler compared to placebo was demonstrated and that there were no suggestions of adverse effects. The Cough-Cold Panel had reviewed this study and stated that "no side effects or evidence of rebound congestion was noted" (41 FR 38312 at 38402). Another study by Connell (Ref. 3), which was not discussed by the Cough-Cold Panel, consisted of a comparison between groups of normal volunteers assigned to active and placebo inhalers (20 active and 10 placebo). Subjects were instructed to use a dose of two inhalations per nostril every 4 hours during the waking hours for a 2-week period. The study concluded that there were no signs of "rebound congestion" in the 20 normal volunteers who used the propylhexedrine inhaler every 4 hours for 2 weeks.

The agency agrees with the Cough-Cold Panel that the first study by Connell (Ref. 1) does suggest rebound congestion. In addition, although no rebound was seen with the single-dose study performed by Hamilton (Ref. 2), this is not sufficient proof that rebound does not occur because rebound is more likely to occur with repeated doses. The second study by Connell (Ref. 3) was intended to measure rebound after use of the propylhexedrine inhaler. Although the study concluded that there were no signs of rebound in 20 normal volunteers, the agency believes it would have been more meaningful if the study had included a number of subjects with nasal congestion associated with head colds or acute coryza as well as some subjects who used the recommended dose of two inhalations every 2 hours for a number of days. Thus, the agency believes that the second Connell study (Ref. 3) does not establish that rebound congestion due to propylhexedrine inhalation under actual use conditions does not occur.

Other references indicate that sympathomimetic amines can cause rebound congestion (Refs. 4 and 5). For example, one source notes that side effects of propylhexedrine include rebound congestion, headache, and, in rare instances, an increase in blood pressure (Ref. 4). Another source states that a major limitation of therapy with nasal decongestants is that loss in efficacy and "rebound" hyperemia and worsening of symptoms often occur with chronic use or when the drug is stopped (Ref. 5).

Regarding the comment's contention that the 3-day use limitation warning is arbitrary and unsubstantiated, the agency concluded in the tentative final monograph that the 3-day warning is justified in view of the Cough-Cold Panel's finding "that nasal decongestants can produce rebound congestion after a short period of use," i.e., 4 to 6 hours; as well as by prolonged use caused by habitual use for varying periods of time (50 FR 2232). Moreover, the agency finds the comment's suggested warning "Not to be used for prolonged periods" to be too vague and indefinite. Because some individuals have a tendency to use topical nasal decongestants for prolonged periods, the agency believes that it is important to specifically state how long the product should be used. Because rebound congestion can occur after a short period of use, the agency believes that a 3-day use limitation provides a reasonable period of time for relief of nasal congestion as well as an adequate margin of safety against the development of rebound congestion. Thus, the comment's recommendation is not being accepted.

The agency has determined that it is important to inform consumers of the consequences of too frequent or prolonged use of propylhexedrine or other topical nasal decongestants. Such products will have to bear the following warning: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." (See also comment 2 in section I.A. of this document and comment 28 in section I.E. of this document.)

References

(1) Connell, J., "Analysis of Study Designed to Characterize 'Benzedrex' Inhaler Response with Nasal Airway Resistance Measurements and Nasal Congestion Ratings," draft of unpublished study, in OTC Vol. 040253.

(2) Hamilton, L., "Analysis of Study Designed to Characterize Propylhexedrine Inhaler Activity as Measured by Nasal Airway Resistance and Nasal Congestion Criteria," draft of unpublished study, in OTC Vol. 040272.

(3) Connell, J., "Analysis of Nasal Airflow Study Designed for the Determination of 'Rebound Congestion' from the 'Benzedrex' Inhaler," draft of unpublished study, in OTC Vol. 040272.

(4) Harvey, S. C., "Sympathomimetic Drugs," in "Remington's Pharmaceutical Sciences," 18th ed., edited by A. R. Gennaro et al., Mack Printing Co., Easton, PA, p. 884, 1990.

(5) Hoffman, B. B., and R. J. Lefkowitz, "Catecholamines and the Sympathomimetic Drugs," in "The Pharmacological Basis of

Therapeutics," 8th ed., edited by A. G. Gilman et al., Pergamon Press, Inc., New York, p. 216, 1990.

II. Summary of Significant Changes From the Proposed Rule

1. In order to allow for flexibility in the labeling of products, the agency has revised the indications in § 341.80(b)(1) to allow manufacturers to choose from among any of the indications (i.e., the common cold (cold), allergic rhinitis, or sinusitis) for nasal decongestant drug products that are consistent with the intended use of the product. (See comment 14 in section I.E. of this document)

2. The agency is not including proposed § 341.80(b)(2), "Other allowable indications" in this final monograph, but is revising and incorporating the statements proposed in that section of the tentative final monograph into the indications included in § 341.80(b)(2) of this final monograph. (See comments 13 and 16 in section I.E. of this document.)

3. Because the phrases "For the temporary relief of" and "Temporarily relieves" are interchangeable, the option of using either phrase is included in § 341.80(b) of the final monograph. (See comment 15 in section I.E. of this document.)

4. The agency is including the term "sinus congestion" in the indications in § 341.80(b)(2)(iv) and (v), and the word "temporarily" has also been added so that the phrase reads: "* * * temporarily relieves sinus congestion and pressure." (See comments 16 and 17 in section I.E. of this document.)

5. In order to conform to numbering specified in 1 CFR 21.11(h), the numbering of many of the warnings proposed in § 341.80(c) has been changed. Specifically, paragraphs (*a*) through (*d*) have been designated as (A) through (D) in this final monograph. Likewise, in the directions proposed in § 341.80(d), paragraphs (*a*) and (*b*) have been designated as (A) and (B).

6. The agency has revised the warning for oral nasal decongestants in proposed § 341.80(c)(1)(i)(*a*) and (c)(1)(ii)(*a*) (designated as § 341.80(c)(1)(i)(A) and (c)(1)(ii)(A) in this final monograph) to provide the information in two separate statements. The agency is also requiring that the first part of the warning appears on the label of the product in boldface type so that the warnings now read as follows: "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor." (See comment 26 in section I.E. of this document.)

7. The agency has revised the warning for oral nasal decongestants in proposed § 341.80(c)(1)(i)(*b*) and (c)(1)(ii)(*b*) (designated as § 341.80(c)(1)(i)(B) and (c)(1)(ii)(B) in this final monograph) to delete the language that restricted use of the product to only 7 days. The revised warning reads as follows: "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor." (See comment 21 in section I.E. of this document.)

8. To be consistent with the wording of other warnings for children, the agency has revised the warning proposed in § 341.80(c)(1)(ii)(*c*) (designated as § 341.80(c)(1)(ii)(C) in this final monograph), "Do not give this product to children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," as follows: "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor." Likewise, the warning proposed in § 341.80(c)(2)(ix)(*b*) (designated as § 341.80(c)(2)(viii)(B) in this final monograph), "Do not use this product in children who have heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor," has been revised as follows: "Do not use this product in a child who has heart disease * * *."

9. The agency has divided the warning for topical nasal decongestants proposed in § 341.80(c)(2)(i)(A) into two separate warnings and is requiring that the first warning appear on the label of the product in boldface type as follows: "Do not exceed recommended dosage." [sentence in boldface type] and "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge." These two warnings are being included in the final monograph in § 341.80(c)(2)(i)(A) and (c)(2)(i)(B), respectively. Inclusion of these two warnings has necessitated a change of proposed § 341.80(c)(2)(i)(*b*) to § 341.80(c)(2)(i)(C). (See comment 27 in section I.E. of this document.)

10. To inform and warn consumers about the possibility of the occurrence of rebound congestion with prolonged and excessive use of topical nasal decongestants, the agency has expanded the warning in proposed § 341.80(c)(2)(iii)(*a*), § 341.80(c)(2)(vi), § 341.80(c)(2)(ix), and § 341.80(c)(2)(x) (designated as § 341.80(c)(2)(iii)(A), § 341.80(c)(2)(v), § 341.80(c)(2)(viii), and § 341.80(c)(2)(ix), respectively, in this final monograph) as follows: "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor." (See comment 2 in section I.A. of this document.)

11. The agency is deleting the warning proposed for 1 percent phenylephrine hydrochloride in § 341.80(c)(2)(v) and is instead requiring that 1 percent phenylephrine bear the warning for all topical nasal decongestants in § 341.80(c)(2)(iii)(A). (See comment 2 in section I.A. of this document and comment 28 in section I.E. of this document.)

12. To be consistent with the drug interaction precaution statement used for OTC antitussive and bronchodilator drug products, the agency has revised § 341.80(c)(1)(i)(*d*) (now designated as § 341.80(c)(1)(i)(D)) to read:

Drug interaction precaution. Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

The drug interaction precaution statement in § 341.80(c)(1)(ii)(*d*) (now designated as § 341.80(c)(1)(ii)(D)) is similarly revised to read:

Drug interaction precaution. Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product.

(See comment 22 in section I.E. of this document.)

13. The agency is adding § 341.80(d)(2)(iv)(A)(*2*) for 0.025-percent aqueous oxymetazoline hydrochloride solution to provide for use by children 2 to under 6 years of age, and removing § 341.90(m). (See comment 8 in section I.C. of this document.)

14. The agency is revising § 341.80(d)(2)(vii)(A)(*2*) for 0.05-percent aqueous xylometazoline hydrochloride solution to provide for use by children 2 to under 6 years of age. The agency also is not including proposed § 341.90(n) in this final monograph. (See comment 8 in section I.C. of this document.)

15. The agency is adding the statement "Use only recommended amount." to the directions for oxymetazoline hydrochloride (§ 341.80(d)(2)(iv)(A)(*2*)), xylometazoline hydrochloride (§ 341.80(d)(2)(vii)(A)(*2*)), and

phenylephrine hydrochloride (§ 341.80(d)(2)(v)(A)(4)) products labeled for use by children 2 to under 6 years of age. The agency is also requiring that such products have either a calibrated dropper or a metered-dose spray that delivers no more than a stated amount of drug per three drops or three sprays. (See comment 8 in section I.C. of this document.)

16. The agency has revised the directions statements, where appropriate, as follows: "Adults and children 12 years of age and over,". The agency has added the phrase "* * * and children 12 years of age and over" to the directions to clarify that the 12 years and over age group should receive an adult dose.

17. The agency is not including proposed § 341.80(e) (which states: "The word 'physician' may be substituted for the word 'doctor' in any of the labeling statements above.") in this final monograph because the agency has amended § 330.1 (21 CFR 330.1) to permit the interchangeability of certain terms, including "physician" and "doctor," in all OTC drug monographs. (See 59 FR 3998, January 28, 1994.)

18. The agency is revising the paragraph designations in § 341.3 *Definitions* in that § 341.3((e) and (f) are being changed to § 345.3(f) and (g), respectively) and is adding new § 341.3(h) for *Calibrated dropper*. (See comment 8 in section I.C. of this document.)

19. The agency has determined that for an active ingredient to be included in an OTC drug final monograph, it is necessary to have publicly available chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. Because l-desoxyephedrine and racephedrine hydrochloride are not currently standardized and characterized for quality and purity in official compendia, i.e., the United States Pharmacopeia (U.S.P.), they are not included in this final monograph. However, should interested parties develop appropriate standards that are included in the U.S.P., this final monograph will be amended to include one or both of these ingredients. In the interim, the final monograph will be reserved for entries for l-desoxyephedrine and racephedrine hydrochloride as topical nasal decongestants. These ingredients are being included in § 310.545(a)(6)(ii)(B), nonmonograph ingredients, until appropriate compendial standards are developed.

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

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC nasal decongestant drug products are generally recognized as safe and effective and not misbranded. Specifically, the following ingredients are included in this final monograph as OTC oral nasal decongestants: Phenylephrine hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate. The following ingredients are included as topical nasal decongestants: Ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, propylhexedrine, and xylometazoline hydrochloride. The status of phenylpropanolamine preparations as an oral nasal decongestant is deferred at this time. All other ingredients for OTC nasal decongestant use in this rulemaking are considered nonmonograph ingredients: Beechwood creosote (topical), bornyl acetate (topical), camphor (topical), cedar leaf oil (topical), l-desoxyephedrine (topical), ephedrine (oral), ephedrine hydrochloride (oral), ephedrine sulfate (oral), racephedrine hydrochloride (oral/topical), eucalyptol/eucalyptus oil (topical), menthol/peppermint oil (topical), allyl isothiocyanate (mustard oil) (topical), thenyldiamine hydrochloride (topical), thymol (topical), and turpentine oil (spirits of turpentine) (topical). The agency has established 21 CFR 310.545 in which it lists certain active ingredients that are not generally recognized as safe and effective for certain OTC drug uses. The following ingredients are presently listed in 21 CFR 310.545(a)(6)(ii) for nasal decongestant drug products: Allyl isothiocyanate, camphor (lozenge), beechwood creosote (oral), eucalyptol (lozenge), eucalyptol (mouthwash), eucalyptus oil (lozenge), eucalyptus oil (mouthwash), menthol (mouthwash), peppermint oil (mouthwash), thenyldiamine hydrochloride, thymol, thymol (lozenge), thymol (mouthwash), and turpentine oil. In this final rule, the agency is amending 21 CFR 310.545(a)(6)(ii) by adding the following nasal decongestant ingredients: Beechwood creosote (topical), bornyl acetate (topical), cedar leaf oil (topical), l-desoxyephedrine (topical), ephedrine (oral), ephedrine hydrochloride (oral), ephedrine sulfate (oral), and racephedrine hydrochloride (oral/topical). These ingredients appear in new § 310.545(a)(6)(ii)(B), while previous § 310.545(a)(6)(ii) is redesignated § 310.545(a)(6)(ii)(A). Any drug product marketed for use as an OTC nasal decongestant that is not in conformance with the monograph (21 CFR part 341, subparts A, B, and C) is considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502 of the act and cannot be marketed for this use unless it is the subject of an approved application. An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 2220 at 2238). FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This final rule will require some relabeling for products containing monograph ingredients. Manufacturers will have 1 year to implement this relabeling. This final rule will also require reformulation of any products containing beechwood creosote (topical), bornyl acetate (topical), cedar leaf oil (topical), l-desoxyephedrine (topical), ephedrine sulfate (oral), and racephedrine hydrochloride (oral/topical). For all other nonmonograph ingredients listed above, the effective date was May 7, 1991. The impact to the final rule appears to be minimal. Accordingly, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the regulatory flexibility Act, no further analysis is required.

The agency is removing existing warning and caution statements in § 369.20 for "NASAL PREPARATIONS: OIL BASE," "NASAL PREPARATIONS

IN PLASTIC SPRAY CONTAINERS," "NASAL PREPARATIONS: VASOCONSTRICTORS (AMPHETAMINE, EPHEDRINE, EPINEPHRINE, METHAMPHETAMINE, AND OTHERS OF SIMILAR ACTIVITY)," "PHENYLEPHRINE HYDROCHLORIDE PREPARATIONS, ORAL" and the terms "PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE" and "AND OTHERS OF SIMILAR ACTIVITY" in the entry "NASAL PREPARATIONS: VASOCONSTRICTORS (PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE, PHENYLPROPANOLAMINE, AND OTHERS OF SIMILAR ACTIVITY)" because these portions of the regulations are superseded by the requirements of the nasal decongestant final monograph (21 CFR part 341).

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 341

Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310, 341, and 369 are amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.545 is amended by redesignating the text of paragraph (a)(6)(ii) as paragraph (a)(6)(ii)(A), by adding new (a)(6)(ii)(A) heading and paragraphs (a)(6)(ii)(B) and (d)(23), and by revising paragraph (d) introductory text and paragraph (d)(1) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(6) * * *

(ii) *Nasal decongestant drug products*—(A) *Approved as of May 7, 1991.* * * *

(B) *Approved as of August 23, 1995.*

Bornyl acetate (topical)
Cedar leaf oil (topical)
Creosote, beechwood (topical)
l-desoxyephedrine (topical)
Ephedrine (oral)
Ephedrine hydrochloride (oral)
Ephedrine sulfate (oral)
Racephedrine hydrochloride (oral/topical)

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(23) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3) through (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(9) through (a)(10)(iii), and (a)(11) through (a)(18)(i) of this section.

* * * * *

(23) August 23, 1995, for products subject to paragraph (a)(6)(ii)(B) of this section.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

4. Section 341.3 is amended by adding new paragraphs (f), (g), and (h) to read as follows:

§ 341.3 Definitions.

* * * * *

(f) *Oral nasal decongestant drug.* A drug that is taken by mouth and acts systemically to reduce nasal congestion caused by acute or chronic rhinitis.

(g) *Topical nasal decongestant drug.* A drug that when applied topically inside the nose, in the form of drops, jellies, or sprays, or when inhaled intranasally reduces nasal congestion caused by acute or chronic rhinitis.

(h) *Calibrated dropper.* A dropper calibrated such that the volume error incurred in measuring any liquid does not exceed 15 percent under normal use conditions.

5. Section 341.20 is added to subpart B to read as follows:

§ 341.20 Nasal decongestant active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage forms established for each ingredient:

(a) *Oral nasal decongestants.* (1) Phenylephrine hydrochloride.

(2) Pseudoephedrine hydrochloride.

(3) Pseudoephedrine sulfate.

(b) *Topical nasal decongestants.* (1) [Reserved]

(2) Ephedrine.

(3) Ephedrine hydrochloride.

(4) Ephedrine sulfate.

(5) [Reserved]

(6) Naphazoline hydrochloride.

(7) Oxymetazoline hydrochloride.

(8) Phenylephrine hydrochloride.

(9) Propylhexedrine.

(10) Xylometazoline hydrochloride.

6. Section 341.80 is added to subpart C to read as follows:

§ 341.80 Labeling of nasal decongestant 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 "nasal decongestant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the phrase listed in paragraph (b)(1) of this section, as appropriate, and may contain any additional phrases listed in paragraph (b)(2) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraphs (b)(1) and (b)(2) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in paragraphs (b)(1) (i), (ii), and (iii) of this section):

(i) "due to" (select one of the following: "the common cold" or "a cold").

(ii) "due to" (select one of the following: "hay fever," "hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)").

(iii) "associated with sinusitis."

(2) In addition to the information identified in paragraph (b)(1) of this section, the labeling of the product may contain any (one or more) of the following statements:

(i) (Select one of the following: "For the temporary relief of" or "Temporarily relieves") (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Select one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; temporarily relieves sinus congestion and pressure."

(v) "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20 (a)(1), (a)(2), and (a)(3) when labeled for adults.* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(D) "*Drug interaction precaution.* Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product."

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20 (a)(1), (a)(2), and (a)(3) when labeled for children under 12 years of age.* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(D) "*Drug interaction precaution.* Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product."

(iii) *For oral nasal decongestant products labeled for both adults and children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(1)(i) of this section.

(2) *Topical nasal decongestants*—(i) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for adults.* (A) "Do not exceed recommended dosage." [sentence in boldface type]

(B) "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge."

(C) "The use of this container by more than one person may spread infection."

(ii) [Reserved]

(iii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20 (b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for adults.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(iv) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6) at a concentration of 0.05 percent.* "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

(v) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(vi) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(2)(i) of this section.

(vii) [Reserved]

(viii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for children under 12 years of age.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product in a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(ix) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(x) *For topical nasal decongestant products labeled for both adults and for children under 12 years of age.* The labeling of the product contains the applicable warnings identified in paragraphs (c)(2)(i), (c)(2)(ii), (c)(2)(iii), and (c)(2)(v) of this section.

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

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride identified in § 341.20(a)(1).* Adults and children 12 years of age and over: 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours. Children 6 to under 12 years of age: 5 milligrams every 4 hours not to exceed 30 milligrams in 24 hours. Children 2 to under 6 years of age: 2.5 milligrams every 4 hours not to exceed 15 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(ii) *For products containing pseudoephedrine hydrochloride or*

pseudoephedrine sulfate identified in § 341.20 (a)(2) and (a)(3). Adults and children 12 years of age and over: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours. Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

(2) *Topical nasal decongestants*—(i) [Reserved]

(ii) *For products containing ephedrine, ephedrine hydrochloride, or ephedrine sulfate identified in § 341.20(b) (2), (3), and (4)*—(A) *Nasal drops or sprays—For a 0.5-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(B) *Nasal jelly—For a 0.5-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours.

(iii) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6)*—(A) *Nasal drops or sprays*—(*1*) *For a 0.05-percent aqueous solution.* Adults and children 12 years of age and over: 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.025-percent aqueous solution.* Children 6 to under 12 years of age (with adult supervision): 1 or 2 drops or sprays in each nostril not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(B) *Nasal jelly*—(*1*) *For a 0.05-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.025-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 6 hours. Children under 6 years of age: consult a doctor.

(iv) *For products containing oxymetazoline hydrochloride identified in § 341.20(b)(7)*—(A) *Nasal drops or sprays*—(*1*) *For a 0.05-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(*2*) *A 0.025-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.027 milligrams of oxymetazoline per three drops or three sprays.* Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Use only recommended amount. Do not exceed 2 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly—For a 0.05-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period. Children under 6 years of age: consult a doctor.

(v) *For products containing phenylephrine hydrochloride identified in § 341.20(b)(8)*—(A) *Nasal drops or sprays*—(*1*) *For a 1-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.5-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*3*) *For a 0.25-percent aqueous solution.* Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(*4*) *A 0.125-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.135 milligrams of phenylephrine per three drops or three sprays.* Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 4 hours. Use only recommended amount. [previous sentence in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly*—(*1*) *For a 1-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *For a 0.5-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*3*) *For a 0.25-percent water-based jelly.* Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours. Children under 6 years of age: consult a doctor.

(vi) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form.* The product delivers in each 800 milliliters of air 0.40 to 0.50 milligrams of propylhexedrine. Adults and children 6 to under 12 years of age (with adult supervision): 2 inhalations in each nostril not more often than every 2 hours. Children under 6 years of age: consult a doctor.

(vii) *For products containing xylometazoline hydrochloride identified in § 341.20(b)(10)*—(A) *Nasal drops or sprays*—(*1*) *For a 0.1-percent aqueous solution.* Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(*2*) *A 0.05-percent aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.054 milligrams of xylometazoline per three drops or three sprays.* Children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Children 2 to under 6 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 8 to 10 hours. Use only recommended amount. Do not exceed 3 doses in any 24-hour period. [previous two sentences in boldface type] Children under 2 years of age: consult a doctor.

(B) *Nasal jelly*—(*1*) *For a 0.1-percent water-based jelly.* Adults and children 12 years of age and over: place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Do not give to children under 12 years of age unless directed by a doctor.

(2) *For a 0.05-percent water-based jelly.* Children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 8 to 10 hours. Children under 6 years of age: consult a doctor.

(viii) *Other required statements—For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form.* (A) "This inhaler is effective for a minimum of 3 months after first use."

(B) "Keep inhaler tightly closed."

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

7. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

8. Section 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entries for "NASAL PREPARATIONS: OIL BASE," "NASAL PREPARATIONS IN PLASTIC SPRAY CONTAINERS," "NASAL PREPARATIONS: VASOCONSTRICTORS (AMPHETAMINE, EPHEDRINE, EPINEPHRINE, METHAMPHETAMINE, AND OTHERS OF SIMILAR ACTIVITY)," "PHENYLEPHRINE HYDROCHLORIDE PREPARATIONS, ORAL," and the terms "PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE" and "AND OTHERS OF SIMILAR ACTIVITY" in the entry "NASAL PREPARATIONS: VASOCONSTRICTORS (PHENYLEPHRINE HYDROCHLORIDE, HYDROXYAMPHETAMINE, PHENYLPROPANOLAMINE, AND OTHERS OF SIMILAR ACTIVITY)."

Dated: August 4, 1994.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 94–20456 Filed 8–22–94; 8:45 am]

BILLING CODE 4160–01–P

federal register

Tuesday
August 23, 1994

Part III

Department of the Interior

Bureau of Indian Affairs
25 CFR Parts 200 and 216

Office of Surface Mining Reclamation and Enforcement
30 CFR Part 710, et al.

Surface Coal Mining and Reclamation Operations; Initial Regulatory Program for Indian Lands; Final Rule

DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

25 CFR Parts 200 and 216

Office of Surface Mining Reclamation and Enforcement

30 CFR Parts 710, 715, 716, 717, and 750

RIN 1029–AB65

Surface Coal Mining and Reclamation Operations; Initial Regulatory Program for Indian Lands

AGENCIES: Bureau of Indian Affairs and Office of Surface Mining Reclamation and Enforcement, Interior.

ACTION: Final rule.

SUMMARY: The Bureau of Indian Affairs (BIA) and the Office of Surface Mining Reclamation and Enforcement (OSM) are amending their regulations to remove the current initial program for Indian lands and revise the existing initial program for non-Indian lands to apply to Indian lands. These amendments enable operators on Indian lands initial program sites, in appropriate circumstances, to reclaim to the latest technical and environmental standards of the permanent program, eliminate inconsistencies between the Indian and non-Indian lands initial programs, ensure equal treatment of operators on Indian and non-Indian lands, and clarify regulatory and compliance ambiguities. This rule also amends the permanent program for Indian lands to reflect the foregoing amendments and revises related information collection provisions.

EFFECTIVE DATE: September 22, 1994.

FOR FURTHER INFORMATION CONTACT: Billie E. Clark, Jr., Branch of Federal and Indian Programs, Office of Surface Mining Reclamation and Enforcement, U.S. Department of the Interior, Brooks Towers, 1020 15th Street, Denver, CO 80202; Telephone: 303–844–2829.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Proposed Rule

On March 22, 1993, the Bureau of Indian Affairs (BIA) and the Office of Surface Mining Reclamation and Enforcement (OSM) of the U.S. Department of the Interior published in the **Federal Register** at 58 FR 15404 a proposed rule to remove the Indian lands initial program at 25 CFR Part 216, Subpart B, and amend the non-Indian lands initial program at 30 CFR Chapter VII, Subchapter B, to cover Indian lands. OSM also proposed to make conforming revisions in the Indian lands permanent program and to revise related information collection provisions.

In the notice, OSM and BIA stated that the proposed rule would, among other things:

(1) Require operators on initial program Indian lands to adhere to the initial program performance standards at 30 CFR Chapter VII, Subchapter B;

(2) Allow such operators to avail themselves of 30 CFR 710.11(e), under which they could choose to meet either the initial program performance standards at 30 CFR Chapter VII, Subchapter B, or counterpart permanent program performance standards at 30 CFR Chapter VII, Subchapter K;

(3) Thereby allow such operators to reclaim to the latest technical and environmental standards of the permanent program; and

(4) Eliminate inconsistencies between the Indian and non-Indian lands initial programs, ensure equal treatment of surface coal mine operators on Indian and non-Indian lands, and clarify regulatory and compliance ambiguities.

The proposed rule provided a public comment period and offered to hold a public hearing. The public comment period closed on April 21, 1993. Two requests for a public hearing were received but later withdrawn, and no hearing was held.

B. History of Affected Provisions

The Surface Mining Control and Reclamation Act of 1977 (SMCRA or the Act), Pub. L. 95–87, as amended, 30 U.S.C. §§ 1201–1328, provides for initial and permanent programs for the regulation by the Secretary of the Interior (the Secretary) of surface coal mining and reclamation operations on Indian lands. The Indian lands initial program is codified in the Federal regulations at 25 CFR Part 216, Subpart B (42 FR 63395, December 16, 1977 and 47 FR 13326, March 30, 1982). The Indian lands permanent program is codified at 30 CFR Part 750 (49 FR 38462, September 28, 1984). SMCRA also provides for initial and permanent programs for the regulation of surface coal mining and reclamation operations on non-Indian lands. The initial program for non-Indian lands is codified in the Federal regulations at 30 CFR Chapter VII, Subchapter B (42 FR 62639, December 13, 1977). Permanent program performance standards for non-Indian lands are codified at 30 CFR Chapter VII, Subchapter K.

As first promulgated, the performance standards of the Indian lands initial program at 25 CFR Part 216, Subpart B, were nearly identical to those of the non-Indian lands initial program at 30 CFR Parts 715 and 716. However, there were differences. The most important difference was that the Indian lands initial program included provisions at 25 CFR 216.112 through 216.114 for tribal involvement in inspection, enforcement, and civil penalty proceedings. Also, the Indian lands initial program did not include provisions, as found in the non-Indian lands initial program at 30 CFR 715.19, governing the use of explosives. Furthermore, except for the provisions governing steep-slope mining at 25 CFR 216.111, the Indian lands initial program did not include special performance standards comparable to those for non-Indian lands at 30 CFR Part 716.

On September 28, 1984 (49 FR 38462), OSM published a rule that, among other things, amended the Indian lands initial program to remove the tribal involvement provisions at 25 CFR 216.112 through 216.114. In the preamble to that rule, OSM stated that those provisions were superseded by the permanent program provisions at 30 CFR Parts 842, 843, and 845. Specific provisions to protect Indian interests were also included in 30 CFR Part 750. See e.g. 30 CFR 750.18. OSM determined that having one set of uniform rules made administration of the Act simpler and more efficient and that the change would cause no undue hardship on non-complying operators (49 FR 38464, September 28, 1984). Hence, the major reason for having separate Indian and non-Indian lands initial programs was eliminated.

On February 14, 1991 (56 FR 6224), OSM amended the non-Indian lands initial program to add a new provision—namely, 30 CFR 710.11(e)—that allows operators on non-Indian lands to meet any counterpart permanent program performance standard at 30 CFR Chapter VII, Subchapter K, in lieu of the initial program performance standard at 30 CFR Chapter VII, Subchapter B. Changes to the Indian lands initial program were deemed to be outside the scope of that rulemaking (56 FR 6224, 6226, February 14, 1991). Thus, while operators of non-Indian lands had the option to meet counterpart permanent program standards in lieu of initial program standards, operators on Indian lands did not have that option.

Although 30 CFR 710.11(e) did not apply to initial program Indian lands, the basis and purpose for the

promulgation of that provision are applicable to Indian lands. In explaining that new provision (56 FR 6224, February 14, 1991), OSM stated:

The Permanent Program rules [require] the latest technical and environmental standards for interpretation of the Act and are the result of more than ten years of experience in implementing the Act. They include many program revisions mandated by courts. However, in cases where the Initial Program performance standards continue to apply, Regulatory Authorities must require operators to comply with all of the earlier standards, even when compliance with Permanent Program standards would ensure implementation of [the Act] or would result in reclamation superior to that which would be achieved under the Initial Program standards.

OSM then described five examples of initial program performance standards that were outdated or for which compliance was impractical. Most of those examples are equally germane to Indian lands.

The Indian lands initial program applies to any person who conducts surface coal mining and reclamation operations on Indian lands on or after December 16, 1977. Although the Indian lands permanent program has been in effect since September 28, 1984, operators on all initial program sites must continue to comply with the Indian lands initial program performance standards, even though compliance with counterpart permanent program performance standards would ensure implementation of the Act and could result in superior reclamation. At the present time, there is only one interim program mine in operation on Indian lands. Interim program sites include sites at which surface coal mining operations were complete prior to June 28, 1985 (eight months following the effective date of the Indian lands permanent program) and to surface coal mining operations operating under an interim authorization pending issuance of a permanent program permit (See 30 CFR 750.11(c)). This rulemaking affects only such sites.

II. Discussion of Final Rule

This rule moves the Indian lands initial program regulations at 25 CFR Part 216.100(b), into a new section, but would not change its substance. Part 216, Subpart B would be deleted as proposed. The rule also amends the permanent program for Indian lands at 30 CFR 750.16 to reflect the foregoing changes. The rule also amends the information collection statements at 30 CFR 716.10, 717.10, and 750.10.

These amendments, among other things, allow operators on Indian lands initial program sites to avail themselves of the provisions of 30 CFR 710.11(e), under which operators may choose to meet either the initial program performance standards at 30 CFR Chapter VII, Subchapter B, or counterpart permanent program performance standards at 30 CFR Chapter VII, Subchapter K.

Removal of 25 CFR Part 216, Subpart B

25 CFR section 216.100(b) provides that the requirements of 25 CFR part 216, Subpart B shall be incorporated in all existing and new contracts entered into for coal mining on Indian lands. Although OSM proposed to delete 25 CFR Part 216, Subpart B, OSM has decided to retain the contents of section 216.100(b) by redesignating the section as section 200.12 *Contract Term Incorporation*, and making a technical revision to reflect the fact that the requirements of Subpart B have been replaced by 30 CFR Part 750. This change reflects the fact that the requirement of 25 CFR section 216.100(b) would not be addressed by the amendments to 30 CFR Chapter VII. Accordingly, the existing requirement of 25 CFR section 216.100(b) is being redesignated without substantive change.

As discussed above, prior to this rule 25 CFR Part 216, Subpart B, comprised the Indian lands initial program. Although 25 CFR Part 216, Subpart B, appears in the BIA regulations at 25 CFR Chapter I, the OSM Director is responsible for administering the Indian lands initial program under the general guidance of the Assistant Secretary for Land and Minerals Management.

The performance standards of 30 CFR Chapter VII, Subchapter B, do not place any additional unreasonable burdens on operators on Indian lands initial program sites about and beyond those found in 25 CFR Part 216, Subpart B. The changes will actually give OSM and operators more flexibility while ensuring compliance with the Act.

Amendments to 30 CFR

As discussed below, the amendments to 30 CFR 710.11(b), 715.11, and 750.16 make the non-Indian lands initial program at 30 CFR Chapter VII, Subchapter B, applicable to Indian lands.

Section 710.11(b)—Applicability

The "Applicability" provisions at 30 CFR 710.11(b) are amended to make the initial program regulations at 30 CFR Chapter VII, Subchapter B, applicable to Indian lands. Specifically, it requires any person who conducts surface coal mining and reclamation operations on Indian lands on or after December 16, 1977, in accordance with 30 CFR 750.11(c), to meet the performance standards of 30 CFR Chapter VII, Subchapter B. This change would, by implication, amend any provision of 30 CFR Chapter VII, Subchapter B, containing a reference to the State as the regulatory authority, to the extent that such reference would be construed as also referring to OSM as the regulatory authority on Indian lands.

This change affects operators on Indian lands initial program sites in three principal ways:

a. Permanent Program Performance Standards in Lieu of Initial Program Performance Standards

The change to 30 CFR 710.11(b) allows operators on Indian lands initial program sites to avail themselves of the provisions of 30 CFR 710.11(e), under which they may choose to meet either the initial program performance standards at 30 CFR Chapter VII, Subchapter B, or counterpart permanent program performance standards at 30 CFR Chapter VII, Subchapter K. Prior to this rulemaking, operators on non-Indian lands were able to avail themselves of section 710.11(e) while operators on Indian lands were not. With this rulemaking, operators on Indian lands may now avail themselves of section 710.11(e). This resolves an inequity. Without the change to section 710.11(b), operators on Indian lands initial program sites could be placed at a competitive and economic disadvantage when compared with operators on non-Indian land, because of performance standards that have been determined to be unnecessary for implementation of SMCRA. Thus, the change to section 710.11(b) eliminates inconsistencies between the current Indian and non-Indian lands initial programs and ensures equal treatment of operators on Indian and non-Indian lands.

This rulemaking will have no cumulative negative environmental effect. Allowing operators to choose compliance with the permanent program performance standards will ensure compliance with the Act. The permanent program performance standards represent the latest technical and environmental standards for interpretation of the Act, and are the result of more than fifteen years of experience in implementing the Act. The permanent program performance standards also include revisions mandated by courts. Hence, the Act will be complied with and environmental

impacts will be fully analyzed and considered before final decisions are reached.

b. Frequency of Inspecting Ponds That Do Not Meet Mine Safety and Health Administration Criteria

The Indian lands initial program at 25 CFR 216.108(e) required that ponds not meeting the size or other criteria of the Mine Safety and Health Administration regulation at 30 CFR 77.216(a) be examined on a weekly basis. In comparison, the non-Indian lands initial program at 30 CFR 715.17(e)(20) allows the regulatory authority to approve a reduction in the number of examinations of these ponds to four times per year. The change to 30 CFR 710.11(b) makes 30 CFR 715.17(e)(20) applicable to Indian lands and, consequently, allows OSM, the regulatory authority for Indian lands, to approve a reduction in the number of examinations of these ponds to four times per year. This change eliminates a competitive and economic disadvantage placed on Indian land operators by reducing the cost to the operator associated with such examinations.

c. Use of Explosives

Section 710(c) of the Act does not specifically require operators on Indian lands initial program sites to comply with subsection 515(b)(15) of the Act concerning the use of explosives. Therefore, the Indian lands initial program promulgated on December 16, 1977 (42 FR 63395) did not include provisions governing the use of explosives. In comparison, section 502(c) of the Act requires operators on non-Indian lands initial program sites to comply with subsection 515(b)(15) of the Act. Consequently, the non-Indian lands initial program at 30 CFR 715.19 includes provisions governing the use of explosives.

By this rulemaking, 30 CFR 710.11(b) is modified and the provisions at 30 CFR 715.19 governing the use of explosives are made applicable to Indian lands initial program sites. Section 710(d) of the Act, however, requires surface coal mine operators on Indian lands, on which such operations are conducted on and after thirty months from August 3, 1977, to comply with all of subsection 515 of the Act, including subsection 515(b)(15). Furthermore, section 710(d) of the Act requires that after the applicable thirty month period, all of the requirements of subsection 515 of the Act must be incorporated in existing and new leases issued for coal on Indian lands. The changes to 30 CFR 710.11(b) in this rulemaking are effective after the applicable 30-month period when operators on Indian lands must comply with all of the requirements of section 515 of the Act, including those concerning explosives. Therefore, 30 CFR 715.19 is made applicable to Indian lands.

Section 715.11—General Obligations

Part 715 of 30 CFR contains general initial program performance standards and includes regulations governing restoration of disturbed areas to suitable postmining land use, backfilling and grading, off-site disposal of spoil and waste materials, topsoil handling, protection of the hydrologic system, construction, inspection, and maintenance of dams, use of explosives, and revegetation. The focus of 30 CFR Part 715 is on lands regulated by the States. The "General obligations" section of this part is modified by adding a new paragraph to clarify that the general performance standards of this part are also applicable to Indian lands. Specifically, paragraph (d) is added to 30 CFR 715.11. OSM had proposed to add a new subparagraph 30 CFR 715.11(d)(1) which specifically clarified that OSM is the regulatory authority for surface coal mining and reclamation operations conducted on Indian lands initial program sites. This has been OSM's position for a number of years (See, e.g., OSM's preambles on September 28, 1984, and May 22, 1989 (54 FR 22182).). OSM has decided not to include this provision in the final rule because it is not necessary. Although such a clarification would have been useful when this program was codified in 25 CFR, such a clarification is unnecessary once the program is codified under 30 CFR, because the provisions of 30 CFR already define "regulatory authority" and specify what entities perform that role. Thus, the decision not to adopt this provision is not intended to be a substantive change from the existing rule or from the proposed rule. The issue of who may act as the regulatory authority under SMCRA on Indian lands is currently the subject of litigation [*Hopi Indian Tribe* v. *Secretary of the Interior*, No. 89–2055–JGP (D.D.C.); *Navajo Nation* v. *Babbitt*, No. 89–2066–JGP (D.D.C.) (consolidated)]. OSM anticipates the issue will be resolved in the context of that litigation.

OSM proposed a new subparagraph 30 CFR 715.11(d)(2). This provision is being renumbered and adopted. 30 CFR 715.11(d)(1). This subparagraph establishes minimum requirements for mine maps. The maps must show as of December 16, 1977, the lands where coal had not yet been removed, and the lands and structures that had been used or disturbed by a surface coal mining operation. This provision essentially duplicates 25 CFR 216.102(b). This is necessary since the effective date of the initial program for Indian lands is December 16, 1977, as opposed to May 3, 1978, for non-Indian lands, and operators still must supply the subject mine maps to OSM.

Subpart B of 25 CFR Part 216 generally requires coordination and consultation with tribes, much the same as 30 CFR Part 715 requires coordination and consultation with States and local governments. Since Subpart B of 25 CFR Part 216 is removed under this rulemaking, OSM proposed to add a provision at 30 CFR 715.11(d)(3) that requires notification of and consultation with tribal governments to the same extent as is required for State and local governments. The provision is being renumbered and adopted as 30 CFR 715.11(d). This provision reflects the important role of tribal governments in the initial program for Indian lands.

The last sentence of 30 CFR 715.11(d)(2) requires OSM to coordinate with the BIA with respect to special requirements relating to the protection of noncoal resources and the Bureau of Land Management (BLM) with respect to the requirements relating to the development, production and recovery of mineral resources. This sentence has been added to the final rulemaking to specifically recognize the responsibilities that the BIA and the BLM have on Indian lands. It essentially establishes the same requirement for the initial program as exists in 30 CFR 750.6 for the permanent program.

Sections 716.1 Through 716.10—Special Performance Standards

30 CFR Chapter VII, Subchapter B, includes provisions governing general obligations (section 716.1), steep-slope mining (section 716.2), mountain-top removal (section 716.3), special bituminous coal mines (section 716.4), anthracite coal mines (section 716.5), coal mines in Alaska (section 716.6), prime farmland (section 716.7), and information collection (section 716.10). The only counterpart to these regulations under 25 CFR Part 216, Subpart B, was the regulations governing steep-slope mining (section 216.111), which duplicates only a portion of the regulations covering steep-slope mining at 30 CFR 716.2. Under the changes made today, the additional requirements of 30 CFR Chapter VII, Subchapter B, also govern

operations on Indian lands initial program sites, as applicable.

Section 750.16—Performance Standards

30 CFR 750.16 is modified to reflect that operators on Indian lands initial program site must comply with the provisions of 30 CFR Chapter VII, Subchapter B. This is necessary since 25 CFR Part 216, Subpart B is removed by this rulemaking.

III. Response to Comments

Comments on the proposed rule were received from four entities: two tribal governments and two members of the coal industry. The proposal to allow operators to meet counterpart permanent program performance standards in lieu of meeting initial program standards was generally supported by all of the commenters. One commenter said that it favored the proposed rule since the rule would place operators on Indian lands on the same footing as operators on non-Indian lands. However, some commenters suggested that the final rule be modified to reflect specific concerns. Responses to comments on specific issues follow.

A. Combining Initial and Permanent Program Performance Standards

As provided in 30 CFR 710.11(e), for surface coal mining and reclamation operations on Indian lands initial program sites this rule allows operators to meet either the initial or the counterpart permanent program performance standards. One commenter asked whether an operator on Indian lands initial program sites could, for a performance standard applicable to a specific activity, meet part of the initial program performance standard and, for the remainder of that standard, meet the permanent program performance standard.

For example, under this rule, Indian lands initial program operations would be subject to the initial program performance standard at 30 CFR 715.19 governing the use of explosives. The counterpart permanent program performance standard is found at 30 CFR 816.61 through 816.68. The requirements of that portion of the initial program standard at 30 CFR 715.19(c) (1) and (2) are different than the counterpart requirements at 30 CFR 816.64(c) (2) and (3) about what an operator must identify in a blasting schedule. The commenter asked whether an operator could meet the permanent program requirements for those two subsections but meet the initial program requirements for the remainder of the performance standard.

The answer is no. While 30 CFR 710.11(e) allows an operator to meet either the initial or the counterpart permanent program performance standard, the operator may not pick and choose selective portions of a comprehensive standard applicable to a particular activity. In the commenter's example, 30 CFR 715.19 contains a comprehensive performance standard governing the use of explosives. Consequently, under 30 CFR 710.11(e), an operator could choose to meet all of the initial program performance standard at section 715.19 or, in the alternative, all of the permanent program performance standard governing the use of explosives at 30 CFR 816.61 through 816.68.

The approach suggested by the commenter would be impracticable to administer and could result in incomplete compliance with the minimum requirements of both the initial and permanent program performance standards. Each operator who elects to meet a permanent program performance standard in lieu of an initial program standard, is responsible for initially determining the extent of the counterpart initial and permanent program standards. OSM will in all cases have the final say regarding the validity of that determination.

B. Effect of Rule on Previously Approved Activities

One commenter was concerned that this rule would necessitate additional review and approval of activities that previously were approved under 25 CFR Part 216, Subpart B. The commenter's concern is unfounded. This rule does not negate any previous approvals given by OSM under the initial program.

One commenter suggested that this rulemaking will lower standards on initial program sites, since some of the permanent program performance standards are less stringent than the initial program performance standards. The commenter stated that the rule change appears to be only for the convenience of the operators and that alone is not a sufficient reason to lower the standards. Recognizing that both programs meet the requirements of the Act, the commenter was also concerned that the rulemaking may result in a cumulative negative effect on tribal lands. The commenter requested that the rule be modified to require OSM to make a finding that compliance with the permanent program performance standards, as opposed to the initial program performance standards, will have no negative effect and/or will not negatively impact the overall environment.

OSM disagrees. This rulemaking is expected to have no cumulative negative effect on tribal lands, for several reasons. Allowing operators to choose compliance with the permanent program performance standards will not be a problem because such compliance would constitute full compliance with the Act. The permanent program performance standards represent the latest technical and environmental standards for interpretation of the Act, and are the result of more than fifteen years of experience in implementing the Act. The permanent program performance standards also include revisions mandated by courts. Operators opting to meet the permanent program standards would be meeting requirements that satisfy the Act. OSM's approval would be required if on an initial program site an operator wished to initiate under permanent program standards an activity that under the initial program requires regulatory authority approval, or if the operator wishes to apply permanent program standards to an activity approved under the initial program; and OSM would be required to ensure compliance with the Act and the National Environmental Policy Act of 1969 (NEPA). Hence, the Act will be complied with and environmental impacts will be fully analyzed and considered before a final decision is reached.

C. OSM Coordination With Other Agencies

One commenter opposed allowing operators the right to choose permanent program performance standards over initial program performance standards without a tribe being given the opportunity to comment on and/or oppose such action. The commenter stated that the government must support the Federal policy of self-determination for tribes. Therefore, a tribe should be consulted and informed of any and all consequences of operators choosing initial program performance standards over permanent program performance standards. The commenter also stated that the tribes were not being treated as an equal to the States. A State, as the regulatory authority under the Act, can choose not to adopt this rule change in its program but a tribe, since OSM is the regulatory authority under the Act, does not have this same option. In addition, a State could adopt a more restrictive rule that would require operators to follow notice and consultation procedures before using a permanent program performance standards on an initial program site. Hence, the commenter requested that the rule provide notice and consultation with

tribes and that the operator on Indian lands initial program sites obtain prior approval from the tribes before using a permanent program performance standard in lieu of an initial program performance standard.

OSM agrees that the tribes will not be able to act as State regulatory authorities may. This is consistent with SMCRA section 710, under which OSM is the regulatory authority for Indian lands. Under section 710, tribes are not authorized to act as the regulatory authority on Indian lands, so tribes may not take the same actions as may be taken by State regulatory authorities under State primacy.

However, OSM disagrees with the commenter's concerns about consultation with tribes. As noted above, if an operator on an Indian lands initial program site chooses to utilize a permanent program performance standard in lieu of an initial program performance standard, and prior approval is required under the initial program for the activity or the operator is proposing modification of a previously approved activity, then the operator must obtain prior approval from OSM prior to conducting such activity. Prior to OSM taking action, tribes as well as other agencies will be consulted with as provided for under this final rule at 30 CFR 715.11(d)(2). Thus, the final rule requires appropriate consultation with tribes.

One commenter suggested that 30 CFR 750.6(a)(3) be amended to give tribal authorities the option of participating in inspections conducted by OSM in order to assist the tribes in their development of regulatory expertise and to prepare the tribes to assume enforcement authority once appropriate legislation is enacted.

In response to this comment, OSM states that the development of tribal regulatory expertise is beyond the scope of this rulemaking. However, it should be noted that as a routine practice OSM invites tribal and other agency officials to accompany inspectors during all Indian mine inspections.

One commenter requested that OSM consult directly with the tribal governments instead of going through the BIA. The commenter suggested that 30 CFR 750.6(d) be modified to reflect this request. The same commenter stated that tribal governments should be consulted in the same manner as State regulatory agencies, whether or not the tribes have their own regulatory programs under SMCRA.

In response to this comment, OSM states that modifying coordination procedures for the permanent program is beyond the scope of this rulemaking. However, it should be recognized that OSM consults directly with tribal governments concerning permanent program matters as required at 30 CFR 750.6(a)(4). In order to ensure that tribal concerns are fully addressed OSM consults with tribal governments on all permitting actions.

D. Tribal and State Laws

One commenter stated that tribes may undertake their own regulatory program, independent of SMCRA. The same commenter proposed that 30 CFR 715.11(a) be amended to require compliance with tribal laws and regulations for coal mining operations on Indian lands and that the provisions of 30 CFR Part 715 that refer to State and local agencies be amended to include tribal agencies. The commenter further requested that the rules reflect that if there is a conflict between State or local laws and tribal laws, with regard to surface coal mining and reclamation operations on Indian lands, that tribal law should control.

In response to this comment, OSM notes that this rulemaking neither addresses the laws and regulatory programs that tribal governments have enacted, or may enact, nor the conflicts which may exist between tribal laws and State and local laws over the regulation of surface coal mining operations on Indian lands and would not affect the applicability of such tribal laws and regulations. Hence, the concerns raised by the commenter are beyond the scope of this rulemaking. The Tribes have raised this issue in the case of *Hopi Indian Tribe* v. *Secretary of the Interior, supra*, and it may be addressed in that proceeding.

IV. Procedural Matters

Federal Paperwork Reduction Act

This rule does not contain collections of information which require approval by the Office of Management and Budget under 44 U.S.C. 3501 *et seq.*

Executive Order 12866, Regulatory Planning and Review

This rule was not subject to Office of Management and Budget Review under Executive Order 12866.

Regulatory Flexibility Act

The U.S. Department of the Interior (DOI) certifies that this document would not have a significant economic effect on a substantial number of small entities under the Regulatory Flexibility Act, 5 U.S.C. 601 *et seq.* This determination is based on the fact the rule would permit an operator to comply with either initial program rules or permanent program rules. All seven existing mines on Indian lands in the states of Arizona, New Mexico, and Montana would be affected.

Executive Order 12778, Civil Justice Reform

This rule has been reviewed under the applicable standards of Section 2(b)(2) of Executive Order 12778, Civil Justice Reform (56 FR 55195). In general, the requirements of Section 2(b)(2) of Executive Order 12778 are covered by the preamble discussion of this rule. Additional remarks follow concerning individual elements of the Executive Order:

A. What is the preemptive effect, if any, to be given to the regulation?

The rule will have no preemptive effect, since it merely substitutes one set of Federal standards for another set, and no State performance standards or other requirements apply.

B. What is the effect on existing Federal law or regulation, if any, including all provisions repealed or modified?

This rule modifies the implementation of SMCRA as described herein, and is not intended to modify the implementation of any other Federal statute. The preceding discussion of this rule specifies the Federal regulatory provisions that are affected by this rule.

C. Does the rule provide a clear and certain legal standard for affected conduct rather than a general standard, while promoting simplification and burden reduction?

The standards established by this rule are as clear and certain as practicable, given the complexity of the topics covered and the mandates of SMCRA. As noted above, the rule will simplify the regulatory process by establishing one set of initial program regulatory provisions for all surface coal mining operations. The rule would also allow surface coal mining operations to choose to comply with permanent program standards which are in some cases less stringent than initial program standards, where OSM has determined that less stringent permanent program standards fully ensure compliance with SMCRA.

D. What is the retroactive effective, if any, to be given to the regulation?

This rule is not intended to have retroactive effect.

E. Are administrative proceedings required before parties may file suit in court? Which proceedings apply? Is the exhaustion of administrative remedies required?

No administrative proceedings are required before parties may file suit in court challenging the provisions of this

rule under section 526(a) of SMCRA, 30 U.S.C. 1276(a).

Prior to any judicial challenge to the application of the rule, however, administrative procedures must be exhausted. Applicable administrative procedures may be found at 43 CFR Part 4.

F. Does the rule define key terms, either explicitly or by reference to other regulations or statutes that explicitly define those items?

Terms which are important to the understanding of this rule are set forth in 30 CFR 700.5, 701.5 and 750.5.

G. Does the rule address other important issues affecting clarity and general draftsmanship of regulations set forth by the Attorney General, with the concurrence of the Director of the Office of Management and Budget, that are determined to be in accordance with the purposes of the Executive Order?

The Attorney General and the Director of the Office of Management and Budget have not issued any guidance on this requirement.

National Environmental Policy Act

OSM has prepared a final environmental assessment (EA), and has made a finding that the proposed rule would not significantly affect the quality of the human environment under section 102(2)(C) of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. 4332(2)(C). A finding of no significant impact (FONSI) has been approved in accordance with OSM procedures under NEPA. The EA is on file in the OSM Administrative Record at the address specified previously (see **ADDRESSES**).

Authors

The principal authors of this proposed rule are Billie E. Clark, Federal and Indian Permitting Branch, Office of Surface Mining Reclamation and Enforcement, Denver, Colorado, and John S. Retrum, Office of the Field Solicitor, U.S. Department of the Interior, Denver, Colorado. Telephone: 303–844–2829 and 303–231–5350, respectively.

List of Subjects

25 CFR Part 200

Environmental protection, Indian lands, Mineral resources, Mines.

25 CFR Part 216

Environmental protection, Indian lands, Mineral resources, Mines.

30 CFR Part 710

Law enforcement, Public health, Reporting and recordkeeping requirements, Safety, Surface mining, Underground mining.

30 CFR Part 715

Environmental protection, Reporting and recordkeeping requirements, Surface mining, Underground mining.

30 CFR Part 716

Special performance standards, Steep-slope mining, Mountaintop removal, Bituminous coal mines, Prime farmlands.

30 CFR Part 717

Environmental protection, Reporting and recordkeeping requirements, Underground mining.

30 CFR Part 750

Indian lands, Intergovernmental relations, Reporting and recordkeeping requirements, Surface mining, Underground mining.

Dated: July 18, 1994.

Bob Armstrong,

Assistant Secretary, Land and Minerals Management.

August 5, 1994.

Ada E. Deer,

Assistant Secretary, Indian Affairs.

Accordingly, 25 CFR parts 200 and 216 and 30 CFR parts 710, 715, 716, 717, and 750 are amended as set forth below:

25 CFR CHAPTER I

PART 200—TERMS AND CONDITIONS: COAL LEASES

1. The authority citation for Part 200 continues to read as follows:

Authority: Pub. L. 95–87 (30 U.S.C. 1201 *et seq.*), as amended.

2. Section 200.12 is added to read as follows:

§ 200.12 Contract term incorporation.

The requirements of 30 CFR Part 750 shall be incorporated in all existing and new contracts entered into for coal mining on Indian lands.

PART 216—SURFACE EXPLORATION, MINING, AND RECLAMATION OF LANDS

3. The authority citation for Part 216 continues to read as follows:

Authority: 34 Stat. 539, 35 Stat. 312; 25 U.S.C. 355 NT; 35 Stat. 781; 25 U.S.C. 396; sec. 1, 49 Stat. 1250; 25 U.S.C. 473a; 49 Stat. 1967, 25 U.S.C. 501, 502; 52 Stat. 347, 25 U.S.C. 396 a–f; 5 U.S.C. 301.

Subpart B—[Removed]

4. Subpart B—Coal Operations, consisting of §§ 216.100–216.111, is removed in its entirety.

30 CFR CHAPTER VII

PART 710—INITIAL REGULATORY PROGRAM

5. The authority citation for Part 710 continues to read as follows:

Authority: 30 U.S.C. 1201 *et seq.*, as amended, and Pub. L. 100–34.

6. In § 710.11, paragraph (b) is revised to read as follows:

§ 710.11 Applicability.

* * * * *

(b) *Operations on Indian lands.* Any person who conducts surface coal mining and reclamation operations on Indian lands on or after December 16, 1977, in accordance with section 750.11(c) of this chapter, or who was otherwise subject to 25 CFR Part 216, Subpart B prior to September 22, 1994; shall comply with the performance standards of this subchapter.

* * * * *

PART 715—GENERAL PERFORMANCE STANDARDS

7. The authority citation for Part 715 continues to read as follows:

Authority: Pub. L. 95–87 (30 U.S.C. 1201 *et seq.*).

8. In § 715.11, paragraph (d) is added to read as follows:

§ 715.11 General obligations.

* * * * *

(d) *Indian lands.* (1) *Mine maps.* Any person conducting surface coal mining and reclamation operations on Indian lands under this part shall submit no fewer than 7 copies of an accurate map of the mine and authorized mining areas at a scale of 1:6000 or larger. The map shall show, as of December 16, 1977, the lands where coal has not yet been removed and the lands and structures that have been used or disturbed to facilitate surface coal mining operations.

(2) *Consultation with tribal governments.* Any requirement in this part for consultation with or notification to State and local governments shall be interpreted as requiring, in like manner, consultation with or notification to tribal governments. OSM shall consult with the Bureau of Indian Affairs with respect to special requirements relating to the protection of noncoal resources and with the Bureau of Land Management with respect to the requirements relating to the development, production, and recovery of mineral resources on Indian lands.

PART 716—SPECIAL PERFORMANCE STANDARDS

9. The authority citation for Part 716 continues to read as follows:

Authority: Sections 201, 501, 527 and 529, Pub. L. 95–87, 91 Stat. 445 (30 U.S.C. 1201).

10. Section 716.10 is revised to read as follows:

§ 716.10 Information collection.

The Office of Management and Budget has determined that the information collection requirements contained in 30 CFR part 716 do not require approval under the Paperwork Reduction Act.

PART 717—UNDERGROUND MINING GENERAL PERFORMANCE STANDARDS

11. The authority citation for Part 717 continues to read as follows:

Authority: Sections 201 and 501, Pub. L. 95–87, 91 Stat. 445 (30 U.S.C. 1201).

12. Section 717.10 is revised to read as follows:

§ 717.10 Information collection.

The Office of Management and Budget has determined that the information collection requirements contained in 30 CFR part 717 do not require approval under the Paperwork Reduction Act.

PART 750—REQUIREMENTS FOR SURFACE COAL MINING AND RECLAMATION OPERATIONS ON INDIAN LANDS

13. The authority citation for Part 750 continues to read as follows:

Authority: Pub. L. 95–87 (30 U.S.C. 1201 *et seq.*, as amended); and Pub. L. 100–34.

14. Section 750.10 is revised to read as follows:

§ 750.10 Information collection.

The Office of Management and Budget has determined that the information collection requirements contained in 30 CFR part 750 do not require approval under the Paperwork Reduction Act.

15. In § 750.16, the second sentence is revised to read as follows:

§ 750.16 Performance Standards.

* * * Prior to that time, the person conducting surface coal mining and reclamation operations shall adhere to the performance standards of 30 CFR Chapter VII, Subchapter B.

[FR Doc. 94–20514 Filed 8–22–94; 8:45 am]

BILLING CODE 4310–05–M

federal register

Tuesday
August 23, 1994

Part IV

Department of the Interior

Bureau of Indian Affairs

Preservation Establishment, Additions, etc.; Seminole Indian Reservation, Florida; Notice

DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

Proclaiming Certain Lands as Part of the Reservation of the Seminole Tribe of Indians of Florida

AGENCY: Bureau of Indian Affairs, Interior.

ACTION: Notice.

SUMMARY: The Assistant Secretary—Indian Affairs proclaimed 39.407 acres, more or less, as an addition to the reservation of the Seminole Tribe of Indians of Florida on July 1, 1994. This notice is published in the exercise of authority delegated by the Secretary of the Interior to the Assistant Secretary—Indian Affairs by 209 DM 8.3a.

FOR FURTHER INFORMATION CONTACT: Alice A. Harwood, Bureau of Indian Affairs, Division of Real Estate Services, Chief, Branch of Technical Services, MS–4522/MIB/Code 220, 1849 C Street NW., Washington, D.C. 20240, telephone (202) 208–3604.

SUPPLEMENTARY INFORMATION: On July 1, 1994, by proclamation issued pursuant to the Act of June 28, 1934 (48 Stat. 986; 25 U.S.C. 467), the following described tracts of land, located in Hillsborough County, Florida, was added to and made a part of the Seminole Indian Reservation of Florida.

Tallahassee Meridian

Hillsborough County, Florida

All of the East ½ of the Northeast ¼ (E½NE¼) of Section 2, Township 29 South, Range 19 East, Hillsborough County, Florida, lying North of Interstate 4 and East of Orient Road, and less the part of the East ½ of the Northeast ¼ (E½NE¼) of Section 2, Township 29 South, Range 19 East, Hillsborough County, Florida, lying Northerly of State Road No. 400 and East of Orient Road, described as follows:

Commencing at the Southwest corner of the North 967.00 feet of the Northeast ¼ of the Northeast ¼ (NE¼NE¼) of said Section 2; thence run South 89°14'33" East, along the South boundary of the North 967.00 feet of said Northeast ¼ of the Northeast ¼ (NE¼NE¼), a distance of 35.47 feet to a point on the East right-of-way line of the 60.00 foot right-of-way for Orient Road for a Point of Beginning; thence continue to run South 89°14'33" East, along the South boundary of the North 967.00 feet, a distance of 526.87 feet to a point; thence run South 00°11'46" West, parallel to the West boundary of the East ½ of the Northeast ¼ (E½NE¼) of Section 2 a distance of 547.28 feet to a point of intersection with the Northerly right-of-way line of State Road No. 400; thence run South 49°12'56" West, along said right-of-way line of State Road No. 400 a distance of 633.60 feet to a point of intersection with the East right-of-way line of Orient Road; thence run the following courses along the East right-of-way line of Orient Road, North 00°00'44" West, a distance of 537.26 feet; thence South 89°59'16" West, a distance of 22.00 feet; thence North 00°00'44" West, a distance of 400.00 feet; thence South 89°59'16" West, a distance of 23.00 feet; thence North 00°00'44" West, a distance of 23.00 feet; thence North 00°00'44" West, a distance of 30.87 feet to the Point of Beginning. Containing 30.818 acres, more or less.

And

That part of the East ½ of the Northeast ¼ (E½NE¼) of Section 2, Township 29 South, Range 19 East, Hillsborough County, Florida, lying Northerly of State Road No. 400 and East of Orient Road, described as follows:

Commencing at the Southwest corner of the North 967.00 feet of the Northeast ¼ of the Northeast ¼ (NE¼NE¼) of said Section 2; thence run South 89°14'33" East, along the South boundary of the North 967.00 feet of said Northeast ¼ of the Northeast ¼ (NE¼NE¼), a distance of 35.47 feet to a point on the East right-of-way line of the 60.00 feet right-of-way for Orient Road for a point of beginning; thence continue to run South 89°14'33" East, along said South boundary of the North 967.00 feet, a distance of 526.87 feet to a point; thence run South 00°11'46" West, parallel to the West boundary of the East ½ of the Northeast ¼ (E½NE¼) of Section 2, a distance of 547.28 feet to a point of intersection with the Northerly right-of-way line of State Road No. 400; thence run South 49°12'56" West, along said right-of-way line of State Road No. 44, a distance of 633.60 feet to a point of intersection with the East right-of-way line of Orient Road; thence run the following courses along the East right-of-way line of Orient Road, North 00°00'44" West, a distance of 537.26 feet; thence South 89°59'16" West, a distance of 22.00 feet; thence North 00°00'44" West, a distance of 400.00 feet; thence South 39°59'16" West, a distance of 23.00 feet; thence North 00°00'44" West, a distance of 30.87 feet to the Point of Beginning. Containing 8.589 acres, more or less.

The above described parcels contain a total of 39.407 acres, more or less, which are subject to all valid rights, reservations, rights-of-way, and easements of record.

Ada E. Deer,

Assistant Secretary, Indian Affairs.

[FR Doc. 94–20679 Filed 8–22–94; 8:45 am]

BILLING CODE 4310–02–M