B. Alternative Treatment Capacity

EPA currently has limited information on available alternative treatment for metals and cyanides. Analysis of the 1981 RIA Mail Survey indicated a limited amount of commercial capacity. However, comments on the proposed California list rule indicate that there have been significant changes in commercial capacity since the 1981 survey. Thus, EPA is requesting information on the volume of available commercial capacity for treatment of metals and cyanides capable of achieving the prohibition levels discussed in this notice. In addition, some commenters have indicated that additional on-site capacity exists that could be used to manage California list wastes that were also generated on-site. Certain facilities may already have on-site treatment systems or may have impoundments satisfying the § 268.4 and RCRA section 3005(j)(11) criteria to handle these California list wastes. In addition, some facilities may be able to expand or upgrade their existing treatment capacity quickly to handle their California list wastes. Thus, EPA is requesting information with respect to on-site treatment capacity, particularly capacity built after 1980. In addition, EPA is also requesting information on the time needed to develop new capacity, especially the time needed to develop large treatment systems. Commenters should address all steps in development of capacity: general planr ing, engineering design and plans, bid solicitation and evaluation, construction and start-up.

C. Possible National Capacity Variances

The greatest volumes of potential California list wastes shown in the 1981 survey are wastewaters managed in surface impoundments. 51 FR 44732. These wastes could require alternative treatment capacity in non-land based units (presumably tanks) or in retrofitted surface impoundments satisfying § 268.4. Commenters to the proposed California list rule have stressed the difficulties in installing alternative treatment systems without substantial delay. EPA has noted that these comments have merit in many cases. If the volumes of metal-bearing and cyanide-containing wastes needing alternative treatment exceed available capacity, the Agency would consider granting national capacity variances.

EPA believes the maximum duration of such a variance would be November 8, 1988, the date on which most interim status surface impoundments must meet minimum technology requirements, or cease receiving, storing or treating hazardous wastes (RCRA section 3005(j)(1)). If affected facilities do not retrofit their surface impoundments to comply with these requirements, these facilities must develop alternative treatment systems on-site (e.g., tank treatment), or transport the wastes off-site for treatment. The Agency expects that facilities which generate certain large volume flows will either retrofit surface impoundments to meet the 3005(j)(1) requirements, or install tank treatment systems as necessary. New capacity developed to comply with the minimum technology requirements, along with existing commercial capacity, should provide sufficient capacity for California list metals and cyanides beyond November 8, 1988. The Agency solicits comments on this tentative conclusion.

VII. Alternative Procedures for Treatability Variances

The Agency noticed for comment in the December 11, 1986 proposed rule the issue of using non-rulemaking procedures for processing treatability variances (§ 268.44). 51 FR 44729. In the recent final rulemaking on California list hazardous wastes (52 FR 25760), the Agency determined that treatment method equivalency petitions (§ 268.42(b)) need not be processed by rulemaking where the relief sought would not have generic applicability and effect. 52 FR 25780. The Agency believes tentatively that this same reasoning could apply to the analogous treatability variance and therefore solicits further comment on the issue of amending § 268.44 so that informal rulemaking procedures are not mandated for all applications.

Dated: July 24, 1987.

J. Winston Porter,

Assistant Administrator.

[FR Doc. 87-17882 Filed 8-11-87; 8:45 am]

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Wednesday
August 12, 1987

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 310, 341, and 369

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 341, and 369

[Docket No. 76N-052T]

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

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) antitussive drug products (drug products used to relieve cough) 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 antitussive drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: August 12, 1988.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

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 this drug class. Interested persons were invited to submit comments by December 8, 1976. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1977.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products is being issued in the following segments: Anticholinergics and expectorants, bronchodilators, antitussives, nasal decongestants, antihistamines, and combinations. The third segment, the tentative final monograph for OTC antitussive drug products, was published in the **Federal Register** of October 19, 1983 (48 FR 48576). Interested persons were invited to file by December 19, 1983, 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 February 14, 1984. New data could have been submitted until October 19, 1984, and comments on the new data until December 19, 1984. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC antitussive drug products.

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 OTC antitussive drug products occurs with the publication of this document, which establishes § § 341.3 (b) and (c), 341.14, 341.74, and 341.90 (b) and (c) for OTC antitussive drug products in Part 341 (established in the **Federal Register** of October 2, 1986; 51 FR 35326).

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC antitussive drug products (48 FR 48576), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register.** Therefore, on or after August 12, 1988, 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. 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 antitussive drug products, four drug manufacturers, two health professionals, and two health care professional societies submitted comments. Copies of the comments received are on public display in the Dockets Management Branch. Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

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-date notice published in the **Federal Register** of August 9, 1972 (37 FR 16029) or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comment on OTC Antitussive Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive regulations. The comment referred to statements on this

issue submitted earlier to other OTC drug rulemaking proceedings.

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

B. Comments on the Switch of Prescription Antitussives to OTC Status

2. Two comments opposed the agency's proposal to reclassify benzonatate from prescription to OTC status and requested that benzonatate remain a prescription drug because of the possibility of oropharyngeal anesthesia if benzonatate is released in the oral cavity. One comment, submitted by the manufacturer of the only benzonatate product on the market, maintained that the warning statement "Swallow without chewing or dissolving in the mouth. May produce temporary numbness if dissolved in the mouth" is not adequate for OTC use of this drug. The comment stated that, although the product has been marketed as a prescription drug for 24 years with minimal adverse reactions, rapid oropharyngeal anesthesia could result in more severe reactions than temporary numbness, such as choking. The comment added that expanded use of benzonatate by the "unsophisticated consumer," not under professional supervision, could further complicate the issue. The other comment contended that the reading and comprehension levels of the consumer are poor and that public compliance is even poorer. It requested that FDA "think long and hard before turning any more oral medications over to the public for use and abuse." One comment agreed with the agency's proposal to reclassify benzonatate from prescription to OTC status but did not provide any additional information in support of its position.

The agency has reviewed the comments and finds a lack of support in switching benzonatate to OTC status. Only three comments were received, two of which opposed the switch. The agency received no comments from the medical and scientific communities or from consumers on this issue. It should be noted that, in 1981, the manufacturer of the only benzonatate products on the market submitted a supplemental new drug application (NDA) that requested OTC status for the product. Subsequently, based upon a careful review of the prescription drug products (i.e., the approved NDA, the 24-year-marketing history, the available adverse reaction reports, and safety and effectiveness data in the scientific literature), the agency proposed the switch of benzonatate from prescription to OTC marketing status in the tentative final monograph for OTC antitussive drug products (48 FR 28591 to 28592). Although recommending Category I status for the ingredient, the agency recognized that benzonatate has a secondary pharmacological effect as a local anesthetic and that oropharyngeal anesthesia may develop rapidly if the ingredient is released in the oral cavity. Therefore, in the tentative final monograph the agency proposed the warning about swallowing the product without chewing or dissolving it in the mouth, as mentioned by one of the comments.

In proposing this switch, the agency did not permit OTC marketing at that time but stated that public comments submitted in response to the proposed switch should be evaluated before OTC marketing began (48 FR 48591). Likewise, the agency held approval of the supplemental NDA in abeyance, until public comments to the proposed change in status were evaluated. Since that time, the manufacturer has withdrawn its supplemental NDA for OTC status for benzonatate, and in a comment responding to the tentative final monograph (Ref. 1) has requested that benzonatate remain available by prescription only. (See summary of comment above.)

Because of the concerns raised over the agency's proposed labeling, the possibility of anaphylactic reactions, and the possibility of oropharyngeal anesthesia occurring if a benzonatate capsule were chewed or dissolved in the mouth, the agency has determined that benzonatate should only be used under professional supervision. Accordingly, the agency concludes that benzonatate should not be available for OTC use.

Reference

(1) Comment No. C00192, Docket No. 76N–052T, Dockets Management Branch.

3. One comment objected to OTC status for chlophedianol hydrochloride because the public's reading and comprehension levels are poor to bad, and public compliance is even poorer. The comment stated that the "typical John Q. Public" believes that if one helps, two is better, and three is a miracle, and concluded that FDA should "think long and hard before turning any more oral medications over to the public for use and abuse."

The agency based its decision to switch chlophedianol hydrochloride from prescription to OTC marketing status as an antitussive drug product on a careful review of the approved NDA, the marketing history, the available adverse reaction reports, and safety and effectiveness data in the scientific literature (48 FR 48578 and 48579). The agency proposed labeling for this ingredient that it considered adequate to inform and protect the consumer and made every effort to provide labeling that is comprehensive, clear, and concise. The agency believes that the consumer is capable of reading, understanding, and following the label warnings and directions proposed for this drug. The agency proposed directions for use for chlophedianol hydrochloride to provide for a dose of the drug every 6 to 8 hours, not to exceed 4 doses in 24 hours. The agency has no reason to believe, and the comment did not offer any data to support its contention, that consumers would take 2 to 3 dosage units of this medication despite labeling directions to the contrary. This comment was the only comment received opposing the proposed OTC status of chlophedianol hydrochloride. The comment did not submit any data indicating that this drug should not be available OTC, and the ingredient is being included in this final monograph.

C. Comments on Specific OTC Antitussive Active Ingredients

4. One comment from the Committee on Drugs of the American Academy of Pediatrics opposed the reclassification of camphor-containing ointments from Category III to Category I. Based upon "scientific understanding of the mechanism of action of established antitussive agents," the comment did not believe that camphor would suppress a cough when applied to the chest and neck. The comment stated that the proposed labeling "rub on the throat and chest a thick layer * * * to help the

vapors rise to reach the nose and mouth" is confusing when considered in conjunction with the proposed warning "Do not take by mouth or place in nostrils." The comment added that skin and mucosal absorption of camphor is well known and that the heavy application of thick layers of camphor subjects the young child to unnecessary risk of toxicity.

A reply comment pointed out that "central action is not the only mechanism for antitussive activity" and stated that "inhalation of the aromatic vapors provides antitussive activity by local or peripheral action, because of the probable local anesthetic/analgesic properties of the aromatics." It added that the latest investigational methods have shown that camphor provides statistically significant reductions in cough, and that FDA reviewed the full reports of these studies, inspected the facilities of the investigators, and reached the same conclusion.

The reply comment stated that there is no justification for banning useful drugs in all dosage forms and concentrations. It recognized the concern regarding accidental ingestion of large overdoses of camphor in camphorated oil by children, but did not agree that the same degree of hazard or mistaken identity applies to the external use of much smaller concentrations of camphor (i.e., 5 percent) in ointment dosage form.

The reply comment included one new study to support the safety of a 5-percent camphor ointment used externally on young children and three new studies to support the safety of a combination drug product containing camphor, eucalyptol, menthol, and thymol used externally in ointment form on young children (Ref. 1). The reply comment added that these studies show that there is no need for the general OTC restriction for children 2 years of age and over in the label warning. The reply comment also stated that current labeling adequately describes directions for use and warnings against "misuse and accidental possession by children." The labeling specifically warns parents to keep the product out of children's reach, not to swallow the product, and not to place it in the nostrils.

The agency notes that the Cough-Cold Panel mentioned several different mechanisms of action by which an antitussive agent suppresses or inhibits cough (41 FR 38338). Among these, an antitussive agent may work directly by diminishing the sensitivity of the cough receptors in the membranes lining the throat and respiratory passages, and it may act indirectly by exerting a soothing action on irritated or inflamed throat tissues. The agency agrees with the reply comment that inhalation of camphor provides antitussive activity by the local or peripheral action of its vapors.

Data from two new studies submitted in response to the advance notice of poroposed rulemaking for OTC cough-cold drug products were reviewed by the agency when preparing the tentative final monograph for OTC antitussive drug products. These data supported the effectiveness of camphor in reducing the number of coughs when compared to a control (48 FR 48579). No data refuting the effectiveness of camphor as an antitussive agent have been submitted, and the agency reaffirms its determination that camphor is an effective topical antitussive agent.

Various panels and the agency have reviewed and evaluated a great deal of data on the safety of camphor at different concentrations in different vehicles. The Advisory Review Panel on OTC Miscellaneous External Drug Products, in its statement concerning OTC drug products containing camphor, published in the **Federal Register** of September 26, 1980 (45 FR 63878), recommentded that the quantity of camphor in OTC drug products be limited to 2.5 percent. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products concluded that camphor is safe for topical use at concentrations up to 11 percent (44 FR 69802 to 69803). After reviewing both Panel reports, the agency stated in the tentative final monograph for OTC external analgesic drug products, published in the **Federal Register** of February 8, 1983 (48 FR 5854), that the camphor concentration in OTC drug products is being limited to 11 percent or lower. In addition, in the **Federal Register** of September 21, 1982 (47 FR 41716), the agency published a final rule declaring camphorated oil products (which contained 20 percent camphor in cottonseed oil) to be new drugs and misbranded because of the potential hazard for poisoning to occur, primarily in infants and young children, based on a large number of accidental ingestions of this product, often mistaken for castor oil, cod liver oil, mineral oil, olive oil, cough medicine, or other drug products. The agency concluded that the benefit from using such products is insignificant when compared to the risk.

The Cough-Cold Panel stated that clinical experience has confirmed that camphor, when applied topically or as an inhalant, is safe in the dose ranges used as an antitussive (41 FR 38344). The agency has found only three reported cases of camphor poisoning due to inhalation or skin absorption (Refs. 2, 3, and 4). In one case, a 15-month-old infant crawled through spirits-of-camphor (containing 10 percent camphor that had been spilled) and subsequently experienced ataxia and brief, generalized, major motor seizures. A year later, the same infant came into contact with a camphorated vaporizer containing 4.81 percent camphor and had another brief major motor seizure. The occurrence of the seizures with two camphor exposures a year apart indicates a specific sensitivity to camphor (Ref. 2). In another case, camphorated oil was applied continually for about 80 hours to the chest of a 2-year-old child. The diagnosis was camphor poisoning, and the child recovered (Ref. 3). The third case was a near fatal incident in a 6-week-old infant after an ointment containing camphor, menthol, and thymol had been rubbed on the infant's chest (Ref. 4). The agency concludes that these three reported nonfatal incidents are not sufficient to demonstrate a lack of safety for 5 percent camphor when used as an antitussive ingredient according to labeling included in this final monograph.

The agency acknowledges that studies have been done to support the safety of using a 5-percent camphor ointment topically on young children (Ref. 1). However, the agency does not agree with the reply comment that the submitted clinical studies demonstrate that the general OTC label warning limiting use of 5 percent camphor in an ointment base to children 2 years of age and older is unnecessary in the labeling of these drug products. In the three reported cases above of camphor poisoning due to inhalation or skin absorption (Refs. 2, 3, and 4), two of the cases, including the near fatality, involved infants under 2 years of age. The reply comment submitted one study in which a 5-percent camphor ointment was applied to 20 newborn babies, ages 6 to 18 days (Ref. 1). The infants were studied for respiratory changes, motor activity, sleep patterns, blood concentrations of camphor, and clinical blood changes. The other studies submitted by the reply comment evaluated the toxic effects of a combination drug product containing camphor, menthol, thymol, and eucalyptol on children and infants (Ref. 1). Although no toxic effects were noted in any of these studies, the agency notes that the studies were performed in the hospital or in pediatric clinics under the close supervision of doctors and nurses. Such use corresponds to the recommended labeling requirement to

consult a doctor before using camphor-containing ointments in children under 2 years of age. The agency does not believe that unlimited use of camphor-containing ointments would be in the public interest and intends to include the 2-year age limit for such products in this final monograph. This age restriction is consistent with the agency's approach to other externally applied drug products containing camphor (48 FR 5869).

The combination drug product mentioned by the reply comment will be addressed in the tentative final monograph for OTC cough-cold combination drug products that will be published in a future issue of the **Federal Register**. Any comments regarding the safety of or age limits for cough-cold combination drug products should be submitted to that rulemaking.

The agency concludes, based on the studies submitted, that the use of a properly labeled ointment containing 4.7 to 5.3 percent camphor as an antitussive agent to be used on the chest and neck, even in a thick layer, poses no threat to the consumer (48 FR 48579). Therefore, the agency is including in this final monograph 4.7 to 5.3 percent camphor in a suitable ointment vehicle as an antitussive agent.

References

(1) Reply Comment No. 3, Docket No. 76N-052T, Dockets Management Branch.

(2) Skoglund, R. R., L. L. Ware, Jr., and J. E. Schanberger, "Prolonged Seizures Due to Contact and Inhalation Exposure to Camphor," *Clinical Pediatrics*, 16:901–902, 1977.

(3) Summers, G. D., "Case of Camphor Poisoning," *British Medical Journal*, 2:1009, 1947.

(4) Dupeyron, J. P., F. Quattrocchi, H. Castaing, and P. Fabiani, "Intoxication Aigue Du Nourrisson Par Application Cutanee D'une Pommade Revulsive Locale et Antiseptique Pulmonaire," *European Journal of Toxicology*, 9:313–320, 1976.

5. One comment stated that the safety of eucalyptus oil requires additional investigation. The comment cited a recent journal article by Courtemanche, Li, and Peterson (Ref. 1) concerning toxicity in children following accidental ingestion of eucalyptus oil and stated that the agency should review this information before developing a final monograph for eucalyptus oil-containing products.

A reply comment from a manufacturer of an antitussive product in an external ointment form stated that the journal article cited above concerned a case of accidental ingestion of 25 milliliters (mL) of reportedly pure eucalyptus oil by a 3-year-old child. The reply comment maintained that although this amount of drug has the potential to produce a severe adverse reaction, it bears no relationship to the amount of eucalyptus oil, i.e., 1.6 percent, found in the ointment product. The reply comment stated that more than eight 6-ounce jars of ointment would have to be consumed in order to ingest the quantity of eucalyptus oil (25 mL) reported in the article, and that the consumption of 48 ounces of ointment by a 3-year-old child is impossible, without even considering the availability of the product and the taste deterrence of the unpalatable petrolatum base. The reply comment concluded that the accidental ingestion of eucalyptus oil, as reported in the article, far exceeds the amount that a child could ingest in an ointment dosage form and that the ingredient is safe in ointment form as an antitussive when used as directed.

The agency has reviewed the Cough-Cold Panel's discussion of the safety of eucalyptus oil (41 FR 38347), the Courtemanche, Li, and Peterson reference cited by the comment (Ref. 1), and additional information by Courtemanche, Li, and Peterson (Ref. 2). The Panel acknowledged that fatalities have occurred following doses of eucalyptus oil as small as 3.5 mL, although recovery has occurred after doses of 20 mL and even 30 mL (41 FR 38347). The Panel believed that the data confirmed the safety of eucalyptus oil as an ointment (1.3 percent), for steam inhalation (1.7 percent), as a lozenge (0.2 to 15 milligrams (mg)), and as a mouthwash (0.9 mg/mL solution), but because effectiveness data were insufficient, eucalyptus oil was classified in Category III.

The article cited by the comment contains a brief review of the signs and symptoms of eucalyptus oil toxicity and the types of treatment that may be used (Ref. 1). The article refers to 13 reports of seizures in children, but provides no details of these cases. An abstract by the same authors notes that a 3-year-old child ingested 25 mL of eucalyptus oil (neat) (Ref. 2). Vomiting followed within 15 minutes. Forty-five minutes later the child was alert, smelled of the oil, had no abnormal respiration, and was given 15 mL of ipecac syrup. During the next 20 minutes, the child's neurologic responses rapidly deteriorated, and the child became unresponsive to pain. A gastric lavage was performed, and within 2 hours the child was awake and oriented; no seizures occurred, and the respiratory status remained normal.

After reviewing the data, the agency agrees with the reply comment that this case of ingestion of 25 mL of pure, undiluted eucalpytus oil should not affect the status of the safety of eucalyptus oil in an ointment form because it is highly unlikely that a child would have access to enough ointment to produce a toxic dose equivalent to the ingestion of 25 mL of pure eucalyptus oil. Likewise, the other dosage forms and concentrations of eucalyptus oil recommended as safe by the Panel contain amounts well below a toxic dose.

Because no data were submitted demonstrating the effectiveness of eucalyptus oil for the uses mentioned above, the ingredient is not included in this final monograph. Eucalyptus oil in combination with other active ingredients will be discussed in the tentative final monograph for OTC cough-cold combination drug products that will be published in a future issue of the **Federal Register**.

References

(1) Courtemanche, N.J., M. Li, and R.G. Peterson, "Coma Following Acute Ingestion of Eucalyptus Oil in a Child," *Veterinary and Human Toxicology*, 25 (Supplement1):46, 1983.

(2) Courtemanche, N. J., M. Li, and R.G. Peterson, "Coma Following Acute Ingestion of Eucalyptus Oil in a Child," *Veterinary and Human Toxicology*, 25:280–281, 1983.

6. One comment requested the agency to place camphor and menthol in Category I as individual OTC antitussive agents for use in a hot steam vaporizer. The comment submitted two new clinical studies to support its request (Refs. 1 and 2).

The agency has reviewed the new data and determined that the two new clinical studies support the reclassification of the individual ingredients camphor and menthol to monograph status as OTC antitussives for use in a hot steam vaporizer at a concentration of 0.05 percent menthol or 0.1 percent camphor in the water of the vaporizer. In the first study (Ref.1), the individual antitussive effect of menthol and camphor vaporized in steam was compared to unmedicated steam. The study involved 40 normal adults (age 18 and older), and cough was induced by citric acid challenge. The data indicated that camphor and menthol produced a statistically significant reduction in cough counts when compared with unmedicated steam at all four post-treatment time points and overall ($p \leq 0.001$).

The second study (Ref. 2) involved 48 adult subjects with chronic bronchitis and was designed to determine the individual antitussive effect of menthol and camphor vaporized in steam as compared with unmedicated steam. The results demonstrated that menthol and camphor were significantly better than

unmedicated steam at reducing cough: menthol at 0 to 30 minutes ($p \leq 0.03$), 2½ to 3 hours ($p \leq 0.01$), and overall, 0 to 3 hours ($p \leq 0.02$); and camphor at 1½ to 2 hours ($p \leq 0.03$), 2½ to 3 hours ($p \leq 0.04$), and overall, 0 to 3 hours ($p \leq 0.06$). The agency concludes that these studies are acceptable to demonstrate the individual antitussive effectiveness of camphor and menthol for use in steam inhalation. Therefore, the agency is including camphor and menthol in the final monograph for OTC antitussive drug products as antitussives for individual use in a hot steam vaporizer at concentrations of 0.05 percent menthol or 0.1 percent camphor in the water of the vaporizer.

In its report, the Cough-Cold Panel recommended the following specific warning for camphor and menthol for use in a steam vaporizer: "For steam inhalation only. Do not take by mouth" (41 FR 38344 and 38351). The agency agrees with the Panel's recommendation and is including this warning in § 341.74(c)(5)(ii) of this final monograph.

The Panel recommended directions for the individual use of camphor and menthol for steam inhalation (41 FR 38344 and 38351). The agency is accepting the Panel's proposed directions for use with the following exceptions. The Panel based its Category III recommendation on the review of data from a study using a combination drug product containing 7 percent camphor and 3.66 percent menthol and recommended that an initial solution of 7 percent camphor or 3.66 percent menthol be used for preparing the final solution for steam inhalation. In the comment's submissions (Refs. 1 and 2), the initial concentrations of the camphor and the menthol solutions that were used in the studies were 6.2 percent and 3.2 percent, respectively. Based on these studies, in this final monograph, the agency is specifying initial concentrations of 6.2 percent camphor or 3.2 percent menthol in the directions for use for steam inhalation.

Additionally, the Panel proposed that 1 tablespoonful of the initial camphor or menthol solutions per quart of water or 2 teaspoonsful per pint of water be used to prepare the final solutions of camphor and menthol. Assuming that a teaspoonful equals 5 mL (Ref. 3), the agency notes that 1½ teaspoonsful of the initial camphor or menthol solutions per pint of water will result in final solutions of 0.1 percent camphor or 0.05 percent menthol. Therefore, in this final monograph, the agency is specifying the use of 1½ teaspoonsful of the initial solutions per pint of water so that the directions for use are more accurate.

The revised Panel's directions for use of camphor for steam inhalation in § 341.14(d)(2)(iv) of this final monograph are as follows: "*For products containing camphor identified in § 341.14(b)(1) for steam inhalation use.* The product contains 6.2 percent camphor. Adults and children 2 to under 12 years of age: add 1 tablespoonful of solution, for each quart of water, directly to the water in a hot steam vaporizer, bowl, or wash basin; or add 1½ teaspoonsful of solution, for each pint of water, to an open container of boiling water. Breathe in the medicated vapors. May be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor." Following these directions will result in a concentration of 0.1 percent camphor in the water of a vaporizer, bowl, or wash basin.

The agency is including in § 341.74(d)(2)(v) of this final monograph the following directions for use of menthol for steam inhalation: "*For products containing menthol identified in § 341.14(b)(2) for steam inhalation use.* The product contains 3.2 percent menthol. Adults and children 2 to under 12 years of age: add 1 tablespoonful of solution, for each quart of water, directly, to the water in a hot steam vaporizer, bowl, or wash basin; or add 1½ teaspoonsful of solution, for each pint of water, to an open container of boiling water. Breathe in the medicated vapors. May be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor." Following these directions will result in a concentration of 0.05 percent menthol in the water of a vaporizer, bowl, or wash basin.

The agency has also revised the definition for topical antitussive drugs in § 341.3(k), redesignated as § 341.3(c), to read "A drug that relieves cough when inhaled after being applied topically to the throat or chest in the form of an ointment or from a steam vaporizer, or when dissolved in the mouth in the form of a lozenge or compressed tablet" to include use of a steam vaporizer for camphor and menthol in this definition.

The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Reply Comment No. RCO04, Docket No. 76N–052T, Dockets Management Branch.

(2) Report No. RPTO02, Docket No. 76N–052T, Dockets Management Branch.

(3) "The United States Pharmacopeia XXI—The National Formulary XVI." United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1352, 1985.

(4) Letter from W. E. Gilbertson, FDA, to E. J. Hanus, Richardson-Vicks, Inc., coded LET090, Docket No. 76N–052T, Dockets Management Branch.

D. Comments on Dosages for OTC Antitussives

7. One comment requested that the agency's proposed minimum effective antitussive dose for menthol in a lozenge or compressed tablet dosage form be reduced from 5 mg to 3 mg. The comment submitted new data (study CRD 81–10) in support of the 3 mg dose for menthol (Ref. 1). In addition, the comment objected to the agency's finding in the tentative final monograph that study CRD 73–8, previously reviewed by the Panel, is not acceptable to prove the antitussive effectiveness of a dosage of less than 5 mg for menthol in a lozenge or compressed tablet dosage form (48 FR 48585). The comment stated that the agency's contention that study CRD 73–8 is unacceptable because menthol was not studied as a single ingredient, i.e., citric acid was included in the test lozenge but was not included in the placebo lozenge, is inappropriate. The comment explained that citric acid should be considered an inactive, not an active, ingredient. In addition, the quantity of citric acid included in each lozenge (26.9 mg) was quite small and would not be expected to have any significant therapeutic effect on cough. The comment further argued that the Panel classified citric acid as an "inactive and/or pharmaceutical necessary ingredient" (41 FR 38318).

The agency has reviewed the data and concludes that they are insufficient to support the antitussive effectiveness of menthol in lozenge or compressed tablet dosage forms at doses of less than 5 mg. Study CRD 73–8 (Ref. 2) was a single-blind, crossover, induced-cough study involving 16 normal adult subjects. The study compared the antitussive effectiveness of lozenges containing 1 mg menthol, citric acid, and lemon flavor in a candy base with a control lozenge of the candy base (containing FD & C Yellow No. 5) without menthol, citric acid, or lemon flavor. Test subjects were given six citric acid aerosol challenges over a 1-hour period at 10-minute intervals after a lozenge had completely dissolved in the subject's mouth. The agency agrees with the comment that in this study citric acid can be considered an inactive ingredient. However, the comment's statistical analysis of the data showed that the menthol lozenge had a significantly greater reduction in coughs than the control lozenge for only two of the six citric acid aerosol challenges (p

< 0.05). In addition, the control lozenge significantly reduced cough counts when compared to baseline cough counts for three of the six citric acid aerosol challenges. The comment stated that a three-way analysis of variance indicated that the menthol lozenge treatment produced a larger overall mean reduction in coughs that was significantly different from the control lozenge ($p < 0.005$). The Panel reviewed this study along with several other induced-cough studies and concluded that none of the studies provided sufficient data to classify menthol as an effective antitussive (41 FR 38350 to 38351). In addition, the Panel determined that induced-cough studies of this kind are not adequate alone to demonstrate the effectiveness of an antitussive ingredient. The agency concurs. Therefore, study CRD 73–8 is inadequate to demonstrate the effectiveness of menthol in a lozenge or compressed tablet at doses of less than 5 mg.

Study CRD 81–10 (Ref. 1) was a single-blind, 3-day crossover study involving 48 patients (age 18 to 66) with chronic cough due to stable bronchopulmonary disease. The study compared the antitussive effectiveness of lozenges containing 3 mg menthol in a candy base, a control lozenge of the candy base without menthol, and a lactose capsule placebo. Coughs and cough components were recorded on tape recorders on three consecutive mornings and afternoons. Baseline cough counts were recorded for 1½ hours each morning and afternoon before medication was given. Medication was then given at hourly intervals for three doses and coughs were recorded for an hour after each dose. On the first day of the study, all patients were given a lactose capsule placebo for each dose. On days two and three, according to a randomized schedule, patients also were given either a lozenge containing 3 mg menthol in a candy base or a control lozenge of the candy base without menthol.

The agency's statistical analysis of the raw data for study CRD 81–10 shows some discrepancies in p-values between those reported by the comment and those calculated by the agency, using the same statistical procedure, i.e., the nonparametric crossover model developed by Koch (Ref. 3). The agency found significant differences between the menthol lozenge and the control lozenge at only 2 out of 14 cough-counting time periods for cough counts and only 1 out of 14 cough-counting time periods for cough component counts in contrast to the comment's statistical analysis that found significant differences between the menthol lozenge and the control lozenge at 3 out of 14 cough-counting time periods for cough counts and 2 out of 14 cough-counting time periods for cough component counts.

The apparent discrepancies may be due to differences in data analysis. While the agency applied Koch's procedure on the actual change in cough and cough component counts from the morning baseline counts to the counts following medication, the comment may have used a logarithmic transformation of the cough and cough component data. The agency believes that the data on the actual change in cough and cough component counts is easier to interpret than those based on a logarithmic scale. Further, because a nonparametric procedure was used to evaluate the data, there is no clear rationale for using a logarithmic transformation of the data for the analysis. In addition, the data showed that, regardless of whether the patients were using lozenges containing 3 mg menthol in a candy base, a control lozenge of the candy base without menthol, or a lactose capsule placebo, patients generally obtained a reduction in both cough counts and cough components during each cough-counting time period and obtained greater reductions in cough counts and cough components in the afternoon than in the morning. Consequently, this study is insufficient to support the antitussive effectiveness of a 3-mg dose of menthol in lozenges or compressed tablets.

The agency concludes that the studies above are inadequate to support the antitussive effectiveness of dosages of less than 5 mg for menthol in lozenges or compressed tablets and is not including dosages less than 5 mg in this final monograph.

The agency's comments and evaluations of the data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Finkel, S., and S. Zuckerman, "Cough Drops" (Study CRD No. 81–10), draft of unpublished study, Comment No. C00193 and Report No. RPT004, Docket No. 76N–052T, Dockets Management Branch.

(2) Packman E.W., "Vicks Cough Drops," (Study CRD No. 73–8), draft of unpublished study, OTC Volume 040257.

(3) Koch, G.G., "Note: The Use of Non-Parametric Methods in the Statistical Analysis of the Two-Period Change-Over Design," *Biometrics*, 28(2):577–584, 1972.

(4) Letter from W.E. Gilbertson, FDA, to E.J. Hanus, Richardson-Vicks, Inc., coded LET092, Docket No. 76N–052T, Dockets Management Branch.

8. Referring to the agency's discussion on benzonatate at 48 FR 48591, one comment expressed concern that the statement "The drug should be marketed in an appropriate dosage form that does not release it into the oral cavity * * *." could be interpreted too restrictively. The comment suggested that the standard for determining if a dosage form is suitable should be whether the quantity of benzonatate released in the oral cavity may cause significant anesthesia, not whether any benzonatate is released in the oral cavity. The comment stated that this dosage form concern should not justify depriving the consumer of the availability of an appropriately formulated liquid dosage form of benzonatate, noting that market research data have established that the consumer prefers a liquid dosage form of antitussive agents over other available dosage forms.

The agency has determined that benzonatate will be available by prescription only, and therefore benzonatate is not included in this final monograph. (See comment 2 above.) Any new dosage form for benzonatate must be the subject of an NDA or a supplemental NDA.

9. One comment requested that the directions for use for OTC oral antitussive drug products proposed in the tentative final monograph be modified to improve: (1) The OTC dosage schedules for adults and for children 2 to 12 years of age and (2) the professional dosage directions for children under 2 years of age. The comment specifically addressed the agency's proposed dosage schedule in § 341.74(d)(1)(iv) for dextromethorphan and dextromethorphan hydrobromide and recommended that the dosage schedules for children under the age of 12 have a greater subdivision of age ranges than the dosage schedules proposed in the tentative final monograph. For children under 12 years, the comment recommended eight weight-based and age-related dosage ranges, with both age and weight ranges specified in the labeling, to replace the agency's two proposed age-based ranges in the dosage schedule for dextromethorphan. In addition, the comment recommended that the dosage range for adults and children over 12 years of age be changed from the agency's proposed 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours, to 20 to 30 mg every 4 to 6 hours. The comment submitted a report and literature references in support of a safe and effective dose range of 0.3 to 0.5 milligram per kilogram (mg/kg) for dextromethorphan and in support of weight-based, age-related dosage

schedules for children under 12 years of age in general (Ref. 1).

The comment contended that its recommended dosage schedule provides the following improvements over the agency's proposed dosage schedule: (1) It consolidates dosages for adults and for children under 12 years of age to a single 4- to 6-hour schedule that brings the dosage within the effective mg/kg dosage range; (2) it provides more age subdivisions for children under 12 years of age to assure more consistent dosage in a particular dosage range; (3) it provides a weight-based dosage schedule for children 2 to under 12 years of age that supplements the age-based dosage schedule; and (4) it provides an age- and weight-based dosage schedule for children under 2 years of age for use by health care professionals.

The comment explained that age-based dosage schedules with wide age ranges are less sensitive to changes and to differences in growth rate than are weight-based schedules. For this reason, dosage schedules that are based on weight, or that are age-related but closely tied to weight, are considered by the professional community to be more accurate for calculating pediatric drug dosages and are commonly used by physicians. In addition, in a report on OTC internal analgesic, antipyretic, and antirheumatic drug products published in the **Federal Register** of July 8, 1977 (42 FR 35346), FDA's Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel) recommended a pediatric dosage schedule for internal analgesics with six age intervals between the ages of 2 to 12 years. These dosing age intervals for internal analgesics were based on pharmacokinetic and clinical data and were designed to provide a more accurate dosage schedule for children that is consistent with weight and growth parameters for this age group. The comment noted that OTC antitussives and internal analgesics are often combined and requested that the agency adopt a children's dosage schedule for antitussives that is similar to and consistent with the dosage schedule for internal analgesics.

Another comment pointed out that although the Internal Analgesic Panel recognized that antitussive/analgesic combination drug products are rational therapy for concurrent symptoms (42 FR 35493), the dosage range proposed by the agency in § 341.74(d)(1)(iv) for dextromethorphan for children 2 to under 12 years of age is incompatible with the pediatric dosage schedule proposed by the Internal Analgesic Panel for aspirin and acetaminophen. The comment argued that the Internal Analgesic Panel's recommended limitation of the maximum daily pediatric doses of aspirin or acetaminophen to no more than 5 daily doses would preclude a combination drug product containing an internal analgesic ingredient and an antitussive ingredient from providing the maximum permitted daily dose of dextromethorphan, and thereby deprive the child of maximum antitussive benefit. The comment presented the following example: a liquid antitussive/analgesic drug product for use by children 2 to under 11 years of age could be given no more than 5 times a day thus delivering a maximum of 50 mg dextromethorphan. Because the permitted maximum daily dose of dextromethorphan is 60 mg, the child would be "deprived" of an additional 10 mg dextromethorphan.

The comment maintained that dextromethorphan has a wide margin of safety. Quoting the Cough-Cold Panel's report and the agency's tentative final monograph, the comment stated that "there have been no fatalities 'even with doses in excess of 100 times the normal adult dose' " (41 FR 38340) and "because of its low order of toxicity, dextromethorphan is probably the safest antitussive presently available" (48 FR 48581). The comment argued that it is both safe and sound therapy to permit the total daily amount of dextromethorphan proposed for children to be administered in 5 rather than 6 does. Therefore, the comment urged that the limitations on the amount of dextromethorphan in a single dose be increased to permit the pediatric patient to obtain the maximum potential 24-hour benefit of both the analgesic ingredient and the dextromethorphan.

The agency concludes that the data submitted by the comment (Ref. 1) do not support changing the adult dosage schedule for dextromethorphan from 10 to 20 mg every 4 hours, or 30 mg every 6 to 8 hours, to 20 to 30 mg every 4 to 6 hours as requested by the comment. The comment itself notes that, although results of clinical trials show that dextromethorphan is superior to a placebo, there is no uniformity among trials with regard to the dosage at which statistical significance was achieved. It cited studies demonstrating that the minimum effective dose ranges from 5 mg to 30 mg and, as shown in multiple dosing trials, from 6 mg three times daily to 20 mg every 4 hours for two doses, and it stated that the discrepancies among these results could be attributed to study design, end point sensitivity, and inter- and intra-patient variability. Additionally, the comment reanalyzed the data from a published study (Ref. 2) to support its contention that 0.3 to 0.5 mg/kg is the optimum dose for dextromethorphan. The agency questions the validity of using the reanalyzed data to establish an effective dose range for dextromethorphan. The study compared the efficacy of 20 mg dextromethorphan to an active placebo (codeine) and a placebo control, and its results indicated that 20 mg of dextromethorphan is equivalent to 20 mg of codeine and both are superior to placebo. The comment reanalyzed the data by dividing the predetermined 20 mg dextromethorphan dose by the lowest and highest patient weight to obtain an effective dosage range of 0.25 to 0.43 mg/kg (revised by the comment to 0.3 to 0.5 mg/kg). However, because no dose other than 20 mg was used, no conclusions other than the effectiveness of the 20 mg dose can be drawn. For example, if a 15 mg dose had been used and had been equally effective, then the calculated effective range of dextromethorphan would have been 0.1 to 0.32 mg/kg. Furthermore, the subject population of this study is so atypical (16 adult patients with chronic cough due to pulmonary tuberculosis, bronchial carcinoma, or obstructive lung disease) that the mg/kg dosage recommendation obtained from this population should not be extrapolated to a normal population.

The dextromethorphan dosage schedule for adults and children over 12 years of age allows for flexibility in dosages so that manufacturers can write directions for combination products that are applicable to all ingredients in the combination. Therefore, in the absence of data to demonstrate that these proposed dosages are not effective or that alternative doses are superior to the proposed doses, the agency is including in this final monograph the dextromethorphan dosage range it proposed for adults and children over 12 years of age in the tentative final monograph for OTC antitussive drug products.

Several comments (Ref. 3) submitted in response to the tentative final monograph for OTC antihistamine drug products published in the **Federal Register** of January 15, 1985 (50 FR 2200) requested that the agency revise pediatric dosages for OTC drug product categories such as internal analgesics, antitussives, nasal decongestants, and antihistamines to provide consistency among these rulemakings. The comments believed that the dosage schedules should provide: (1) Relatively

fixed dosage forms, (2) sufficient flexibility in the dosage schedules by basing the schedules on weight and age, (3) the ability to correlate dosing with a greater subdivision of standard age breaks, and (4) ease of physician and consumer use.

Because several OTC drug rulemakings could be affected if pediatric dosages are revised, the agency has decided to publish a separate document discussing pediatric dosages for OTC drug products and to defer all issues regarding pediatric dosages to that document. Therefore, the portions of this comment regarding a weight-based, age-related pediatric dosage schedule for dextromethorphan and the pediatric dosage for dextromethorphan when combined with an internal analgesic will be addressed in a future issue of the **Federal Register**. Thus, the dosage schedule for dextromethorphan proposed in the tentative final monograph is included in this final monograph. Should pediatric dosage schedules, in general, be revised in the future, this monograph will be amended accordingly.

References

(1) Comment No. C00197 and Correction No. CR0005, Docket No. 76N–052T, Dockets Management Branch.

(2) Matthys, H., B. Bleicher, and U. Bleicher, "Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough," *Journal of Internal Medicine Research*, 11:92–100, 1983.

(3) Comment Nos. C00201, C00208, C00210, and C00211, Docket No. 76N–052H, Dockets Management Branch.

10. One comment requested clarification of the professional labeling section (§ 341.90(p)(3), redesignated as §341.90(c)(3)) concerning the distribution of a calibrated dispensing device to ensure accurate dosing when OTC drug products containing codeine are used in children 2 to under 6 years of age (48 FR 48595). The comment stated that it assumed "that the scope and intent of [this] section is limited to professional labeling instructions which the dispensing professional is to provide (along with the calibrated device) to a responsible adult at the time the product is delivered for use." The comment stated that it also assumed that it is not the intent of the proposed labeling to require marketers of codeine preparations to include calibrated dispensing devices with each package of their products. The comment stated that the use of codeine products in children under 6 years of age constitutes a small percentage of the total use of these products and argued that a requirement to include a dispensing device with all codeine products would unnecessarily increase the cost of these drug products to all consumers. The comment stated that calibrated dispensing devices are commercially available to pharmacists and other health care professionals. The comment suggested that the professional labeling be amended to require that health care professionals who dispense codeine preparations for use by children under age 6 provide the calibrated dispensing devices at the time the drug is dispensed. The comment also requested that § 341.90(p)(3) be amended to clarify that FDA intends for marketers of codeine preparations to include professional labeling instructions with their products that the dispensing professional must provide when use of the product will be by children under 6.

The comment correctly states that the agency did not intend that dispensing devices calibrated by age or weight for use in children 2 to under 6 years of age be included in each OTC package of codeine drug products. The inclusion of such devices could imply that OTC use of these products in children under 6 years of age is appropriate without the supervision of a physician. However, the comment erred in assuming that FDA intends for marketers of codeine preparations to include labeling instructions with their products that the dispensing professional "must" provide when the product will be used by children under 6 years of age. The agency intends for marketers of codeine preparations to provide to health professionals (e.g., doctors and pharmacists) the specific dosage information on codeine preparations provided in § 341.90(p)(1), redesignated as § 341.90(c)(1). This information in § 341.90(c)(1) can be provided in a written form that the health care professional can give to the child's parent, or the health care professional can provide the information orally to the parent. Such information should be provided to the consumer only when a physician has recommended the use of the product for a child 2 to under 6 years of age.

Once the dosing information has been provided to a parent, the agency intends for the health care professional either to provide a dispensing device directly to the parent or to instruct the parent to obtain a dispensing device to administer the product. The agency emphasizes that if a manufacturer promotes to health care professionals the use of its codeine antitussive drug product in the 2 to under 6 years of age population, the manufacturer must relate the dosages specified in § 341.90(c)(1) of this monography either to a dispensing device specifically designed for use with its product, or to the use of commercially available calibrated dispensing devices, to ensure that dosages for children 2 to under 6 years of age are measured accurately.

In order to make this intent clear, the agency is revising § 341.90(p)(2), redesignated as § 341.90(c)(2), to read: "Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not to exceed the recommended daily dosage" and is adding to § 341.90(p)(1), redesignated as § 341.90(c)(1), the statement "the manufacturer must relate these dosages for its specific product to the use of the calibrated measuring device discussed in paragraph (3) of this section." Also, § 341.90(p)(3), redesignated as § 341.90(c)(3), is revised to read "A dispensing device (such as a dropper calibrated for age or weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose."

The agency is also expanding the portion of the required OTC labeling directions in § 341.74(d)(1)(ii) for the antitussive use of codeine preparations concerning children under 6 years of age to read: "Children under 6 years of age: Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could result in serious side effects for your child." The agency believes that the additional information will ensure that parents will obtain and use a calibrated measuring device when codeine products are recommended for use in the 2– to under 6–year age group, just as calibrated measuring devices are used with other products, e.g., prescription liquid antibiotic products, intended for use in this age group.

E. Comments on OTC Antitussive Labeling

11. One comment noted its continuing position that FDA cannot legally and should not, as a matter of policy, prescribe exclusive lists of terms from which indications for use for OTC drugs must be drawn, and should not prohibit alternative OTC labeling terminology to describe indications which are truthful, not misleading, and intelligible to the consumer. This comment's views were presented in oral and written testimony submitted to FDA in connection with the September 29, 1982, FDA hearing on the exclusivity policy.

The comment stated that the agency's proposed "other allowable statements" are in fact indications that are not required. The comment contended that these allowable statements are beneficial to consumers in choosing a product appropriate for their symptoms and should be permitted in direct conjunction with approved labeling indications.

A second comment believed that proposed § 341.74 would unnecessarily limit the truthful and not misleading language permitted in labeling for antitussive drug products whether the antitussive is used alone or in combination with a second Category I ingredient from a second pharmacological class. This comment added that the agency's effort to implement the exclusivity policy, by providing in § 341.74(b)(2) for optional alternative statements, does not adequately address the legal problems associated with the exclusivity policy inasmuch as there would remain a preclusion against truthful and not misleading statements. The comment, therefore, suggested that § 341.74 be revised to indicate that the alternative statements set forth in this section be considered to be examples of acceptable alternatives and not a legally binding exclusive list. The comment claimed that such a revision can be accomplished by amending the first paragraph of § 341.74(b)(2) to read:

"*Other Allowable Statements.* In addition to the required information identified in paragraph (b)(1) of this section, the labeling of the product may contain any of the following statements or any similar statement which is neither false nor misleading, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information."

A third comment stated that the labeling indications in the tentative final monograph are more restrictive than those recommended by the Panel because the indications are limited to the single phrase "temporarily alleviates * * * cough due to minor throat and bronchial irritation as may occur with * * the common cold * * * or inhaled irritants." Therefore, the comment urged that the "other allowable statements" in the tentative final monograph as well as other alternative language suggested by the comment be permitted for use under the heading "Indications" in place of or in addition to the statement above to allow more flexibility and consumer-oriented language in labeling. (See comment 13 below.)

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 the final rule, 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 required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph.

In the tentative final monograph (48 FR 48593 to 48594), supplemental language relating to indications had been proposed and captioned as *Other Allowable Statements*. 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 proposed in § 341.74(b)(2) in the tentative final monograph for antitussive drug products 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. In this case, the agency has incorporated all of the "Other Allowable Statements" proposed in § 341.74(b)(2) of the tentative final monograph in the indications section in this final monograph. (See also comment 12 below).

12. Referring to the "other allowable statement" proposed for antitussives in § 341.74(b)(2)(v) of the tentative final monograph, "alleviates * * * cough * * * to help you get to sleep," one comment proposed that the following alternate phrases also be permitted to make this phrase more meaningful to consumers: "Alleviates * * * cough * * * to let you sleep," and "alleviates * * * cough * * * to let you rest."

The agency agrees that the two statements proposed by the comment (i.e., alleviates * * * cough * * * to let you sleep," and "alleviates * * * cough * * * to let you rest") are merely alternative ways of saying "alleviates * * * cough * * * to help you get to sleep" which appears in § 341.74(b)(2)(v) of the tentative final monograph and are truthful and not misleading statements. However, the agency prefers to use the word "help" instead of "let" for consistency with the previously proposed indication and with the indications used in the final rule for OTC nighttime sleep-aid drug products. Accordingly, the agency is revising the indication by adding the terms "to help you sleep" and "to help you rest" as follows: (Select one of the following: "Alleviates," "Controls," "Decreases," "Reduces," "Relieves," or "Suppresses") (select one of the following: "Cough," "the impulse to cough," or "your cough") "to help you" (select one of the following: "get to sleep," "sleep," or "rest") and is including the revised indication in § 341.74(b)(3)(v) of this final monograph. (See comment 11 above.)

13. Recognizing and appreciating the agency's effort to provide alternative wording in the indications statement set forth in § 341.74(b), one comment urged FDA to also recognize the use of phrases such as "occurring with" or "associated with" instead of "as may occur with." In addition, the comment believed that flexibility must be allowed in the expression of indications for antitussives because many products containing antitussive ingredients are combinations and thus label space is often limited. The comment maintained that the indications section should recognize not only alternative wording but also alternative indications and suggested the following example: "temporarily (followed by one of the permitted alternatives) cough due to minor throat and bronchial irritations/or cough due to minor bronchial irritation/or cough 'occurring'/'associated with the common cold' or 'a cold' or 'inhaled irritants.'"

The agency agrees with the comment that the phrases "occurring with," "associated with," or "as may occur with" may be used interchangeably. The agency also agrees with the comment that flexibility in the expression of antitussive indications is desirable.

Therefore, in this final monograph, the agency is revising the statement of indications in § 341.74(b) to include two indications as follows: (1) "Temporarily" (select one of the following: "alternatives," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough due to" (select one of the following: "minor bronchial irritation" or "minor throat and bronchial irritation") (select one of the following: "As may occur with," "associated with," or "occurring with") (select one of the following: "a cold" or "the common cold") or "inhaled irritants."

(2) "Temporarily," (select one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough" (select one of the following: "as may occur with," "associated with," or "occurring with") (select one of the following: "A cold," or "the common cold," or "inhaled irritants").

14. One comment objected to the "restrictive nature" of proposed § 341.74(a) in limiting statements of identity for cough medicines to "cough suppressant" or "antitussive (cough suppressant)." The comment urged FDA to allow manufacturers the alternative ways of describing the statement of identity that are set forth in the agency's regulations in 21 CFR 21.61, which require that the label include the established name of the drug, if any, followed by an accurate statement of the general pharmacologic category(ies) of the drug or the principal intended action(s) of the drug, and which provide that, if the drug is a combination that has no established name, the statement of identity may be a prominent and conspicuous statement of the general pharmacological action(s) of the combination or its principal intended action(s) in terms that are meaningful to laymen.

Although recognizing that the term "cough suppressant" is a valid statement of identity for antitussive drug products, the comment stated that an alternative statement such as "controls cough" is as accurate and meaningful a statement of the principal intended actions of these drugs. The comment further contended that the term "antitussive" is descriptive of the general pharmacological category and is equivalent to terms such as "decongestant," "analgesic," and "antihistamine," which are used as examples in § 201.61(b). The comment emphasized the importance of a concise and consistent statement of identity, particularly for drug ingredients used in combination drug products. The comment therefore requested that the proposed statement of identity in § 341.74(a) be amended to allow the term "antitussive" with or without the addition of the term "cough suppressant." The comment also suggested that the phrases "controls non-productive cough," "reduces dry, hacking cough," and "calms and controls dry coughing," etc., are appropriate statements of identity for combination drug products containing an antitussive agent and an expectorant active ingredient.

Although the term "antitussive" accurately describes the pharmacological category of such drugs, the agency believes, as discussed in the tentative final monograph on OTC antitussive drug products (48 FR 48591), that the term "cough suppressant" alone or in conjunction with the term "antitussive" will be better understood by consumers than the term "antitussive" alone. The agency believes that the statements of identity proposed in the tentative final monograph are concise, not confusing, and well recognized by the consumer, and the use of such terms is appropriate in the labeling of combination drug products containing an antitussive and other ingredients. In addition, whenever possible, the agency prefers to use the general pharmacologic category as the statement of identity because information on the principal intended action of the drug product is provided in the indications section of the label. In this case, the wording "controls cough," requested by the comment as a statement of identity, appears in the indications included in § 341.74(b). In instances where the term that describes the pharmacologic category is not appropriate as a statement of identity, the term for the principal intended action is used. For example, the statement of identity for an antihistamine used as an OTC nighttime sleep-aid is "nighttime sleep-aid." For these reasons, the agency has not included the comment's recommended change in the statement of identity. The option of using either "antitussive (cough suppressant)" or "cough suppressant" as the statement of identity, as proposed in the tentative final monograph, is included in this final monograph.

Regarding the comment's recommended statements of identity for a combination of an antitussive active ingredient and an expectorant active ingredient, the agency notes that, to minimize consumer confusion about the labeling of similar marketed products, the labeling of any combination product must contain the statement of identity that is designated in the monograph for each pharmacologic group in the combination product, e.g., "cough suppressant/expectorant." The phrases recommended by the comment, "controls non-productive cough," "reduces dry, hacking cough," and "calms and controls dry coughing," are not statements of identity but are descriptive phrases related to the indications of antitussive drug products. They may appear elsewhere in the labeling of an OTC antitussive drug product (but may not appear in any portion of the labeling required by the monograph and may not detract from such required information) provided they meet the provisions of section 502 of the act (21 U.S.C. 352) relating to misbranding.

15. One comment from a pediatrician stated that the tentative final monograph implies that children under 2 years of age may be most vulnerable to codeine and should not be given the drug; however, nowhere in the labeling for codeine is there a warning against use in children under 2 years of age. The comment emphasized that it is essential that the labeling state that codeine preparations are "totally unsuitable for infants under the age of 2," and added that the proposed statement "consult a doctor" is inadequate. The comment maintained that the vast majority of physicians, other than trained pediatricians, are not aware of the hazards of codeine, and that if a warning against the use of codeine in children under 2 years is not included in the labeling, there may be a continuance of annual deaths in infants due to codeine's respiratory depressant effects.

The agency agrees with the comment that codeine preparations can be hazardous when used in very young children. A review of adverse reactions reported to FDA from the years 1969 to June 1986 reveals eight cases of respiratory depression, apnea, coma, or death associated with the use of codeine-containing drug products in children ranging in age from 3 months to 2½ years (Ref. 1). The agency discussed that hazards of codeine in children in the tentative final monograph on OTC antitussive drug products and proposed that the label of codeine preparations for OTC use limit use to children 6 years of age and over (48 FR 48587). Thus, the label does not provide dosage information for children under 6 years, but states that a doctor must be consulted. The use of codeine in children 2 to under 6 years of age is limited to the supervision of a physician, and dosage information for this age

group is contained in the professional labeling section of the monograph (§ 341.90) (48 FR 48588 and 48595). However, no dosage information regarding the use of codeine in children under 2 years was included in § 341.90 in the tentative final monograph.

Professional labeling is provided to health professionals, but not to the general public. Because health professionals only will be provided with dosage instructions for the use of codeine in children under 6 years, the agency believes that a statement concerning use of codeine in children under 2 years of age should also be included under professional labeling in § 341.90. Such a statement will adequately warn health professionals about the hazards of codeine use in very young children. Therefore, the agency is including the following statement in § 341.90(c)(4): "Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death."

Reference

(1) Department of Health and Human Services, Food and Drug Administration, "Annual Adverse Reaction Summary Listings for the Years 1969 to June 1986," OTC Volume 04TFM, Docket No. 76N-052T, Dockets Management Branch.

16. One comment contended that the warning statements for antitussives proposed in § 341.74(c)(1) (i) and (ii) and (2) (i) and (ii) (48 FR 48594) are both difficult to understand and redundant. Referring to the limited labeling space available, the comment proposed that these warning statements could be shortened, as follows, to more simply and clearly communication the warning information to consumers, while still reflecting the valid medical warnings:

(1) For adults—"Do not take this product for chronic cough such as occurs with smoking, asthma, or emphysema. If cough persists for more than one week, or recurs frequently, or is accompanied by excessive mucus, high fever, rash or stubborn headache, consult a doctor."

(2) For children—"Do not administer this product for chronic cough such as occurs with asthma. If cough persists for more than one week, or recurs frequently, or is accompanied by excessive mucus, high fever, rash or stubborn headache, consult a doctor."

The agency believes that the warnings proposed in § 341.74(c)(1) (i) and (ii) and (2) (i) and (ii) are neither difficult to understand nor redundant. The proposed warnings provide necessary information for the consumer to safely and effectively use OTC antitussive drug products. Further, the labeling proposed for these products is not excessive, and there should be adequate labeling space to list the required information on the product label.

The agency has evaluated the revised warnings suggested by the comment and concludes that the warnings are not sufficiently clear and informative. For example, the warning proposed in § 341.74(c)(1)(i) states, "Do not take * * * for persistent or chronic cough * * * or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor." The revision moves the phrase "cough accompanied by excessive mucus" from the "do not take" restriction and includes it in the second sentence of the warning where there is no such restriction. Thus, this revision changes the intent of the warning and makes it inconsistent with the Panel's recommendations. The Panel discussed conditions in which there is an overproduction of secretions which accumulate in the airway and produce thick sputum (41 FR 38338). Because the suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful, the Panel recommended that antitussives not be used under such conditions, unless specifically directed by a doctor. The agency agrees with the Panel and believes that consumers should be warned against self-treatment of cough with an antitussive when cough is accompanied by excessive mucus; thus, the restrictive labeling "Do not take" is necessary.

The agency's proposed warning includes the term "phlegm (mucus)." The word "phlegm" is not included in the comment's revision. The agency believes that both terms should be included in the warning because consumers do not always use the terms interchangeably and both terms are helpful to make the warning clearer to consumers. The comment's revision also eliminates the word "persistent" from the first part of the warning. The agency believes that "persistent" should remain, in addition to "chronic," because the two words more broadly describe the type of cough for which OTC antitussives should not be used without consulting a doctor.

Additionally, the comment's revision "Do not take this product for chronic cough such as occurs with smoking, asthma, or emphysema" is a direct restriction against the use of antitussive drugs in persons with these conditions. However, the agency's version includes the phrase "unless directed by a doctor," thus informing persons with these conditions that OTC antitussives might be used under a doctor's supervision.

For the warning proposed in paragraph (ii), the comment's suggested revision eliminates entirely the sentence "A persistent cough may be a sign of a serious condition." The agency believes that this statement provides important information, helps to discourage self-treatment of a continuous, lingering cough with OTC antitussive drug products, and should be retained.

The proposed term "tends to recur" has a wider scope than "recurs frequently," the phrase suggested by the comment. The phrase "tends to recur" is broader because it encompasses coughs that may occur very frequently (e.g., every few days or weeks) to those that occur less often, but still on a relatively frequent basis (e.g., every 1 or 2 months). An individual with any type of cough that tends to recur, whether very frequently or less frequently, should consult a physician. Therefore, the agency is retaining the term "tends to recur." The agency also believes that the phrase "persistent headache" is more commonly used and will be better understood by consumers than the comment's suggested term "stubborn headache."

With regard to the warning for antitussives labeled for children under 12 years of age, the agency believes that although the comment's use of the word "administer" is correct, the word "give" is simpler, shorter, and more easily understood. Therefore, the word "give" is being used in the labeling.

For the reasons above, the comment's suggested revisions are not accepted, and the warnings for antitussives proposed in the tentative final monograph are being included in this final monograph.

17. One comment objected to the proposed elimination of the term "caution(s)" in the labeling of OTC drug products. The comment claimed that to the lay consumer there is a distinct difference between the term "warning(s)" and the term "caution(s)." The comment claimed that a warning precludes use of a product under certain conditions, whereas a caution does not preclude use, but may often alert the consumer to a potential problem, e.g., "Caution: If irritation develops discontinue use and consult a physician." Thus, the word "warning" is harsher than the word "caution." The comment asserted that a "caution" may also be used to add emphasis, e.g., "Caution: Use only as directed." The comment argued that it would undoubtedly dilute the impact of essential warning statements if

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

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

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

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. 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.

II. Summary of Significant Changes From the Proposed Rule

1. The agency has determined that benzonatate should not be available for OTC use because of the negative comments received, the possible hypersensitivity reactions to the drug, including potential anaphylactic reactions, and possible paralysis of the oropharyngeal area. Therefore, benzonatate is not included in this final monograph. (See comments 2 and 8 above.)

2. In order to allow for flexibility in the expression of antitussive indications, the agency is revising and expanding the statement of indications in § 341.74(b) to include two indications as follows: (1) "Temporarily" (select one of the following: "Alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough due to" (select one of the following: "minor bronchial irritation" or "minor throat and bronchial irritation") (select one of the following: "as may occur with," "associated with," or "occurring with,") (select one of the following: "a cold" or "the common cold") or "inhaled irritants."

(2) "Temporarily" (select one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough" (select one of the following: "as may occur with," "associated with," or "occurring with") (select one of the following: "a cold," "the common cold," or "inhaled irritants"). (See comment 13 above.)

3. The agency is not including proposed § 341.74(b)(2), *Other allowable statements*, in this final monograph but is revising and incorporating the statements proposed in that section of the tentative final monograph (except for the statements pertaining to benzonatate in § 341.74(b)(3)(vii)) in the indications section in this final monograph. (See comments 11 and 12 above.)

4. The panel recommended placing camphor and menthol for steam inhalation in Category III because there were insufficient data to demonstrate effectiveness. The agency has reviewed new data and determined that the clinical studies support the reclassification of the individual ingredients from nonmonograph to monograph status as OTC antitussives for steam inhalation. Because the agency agrees with the Panel's recommendation concerning the warning for using camphor and menthol in a steam vaporizer, the agency is including the statement, "For steam inhalation only. Do not take by mouth," in § 341.74(c)(5)(ii) in this final monograph. The agency is also including directions for use of camphor and menthol individually in a hot steam vaporizer in § § 341.74(d)(2) (iv) and (v) in this final monograph. In addition, the agency has revised the definition for *"Topical antitussive drug"* in § 341.3(k), redesignated as § 341.3(c), to include use of a steam vaporizer for camphor and menthol in this final monograph. (See comment 6 above.)

5. The agency has revised and combined several warnings in § 341.74(c) that were proposed as separate warnings for products labeled for use only in children under 12 years of age, for use only in adults, or for use in adults and children under 12 years of age. The agency has revised and combined these warnings for clarity and to eliminate unnecessary repetition of warnings in the monograph. This change in format has also resulted in deletion of the proposed section entitled *"For antitussive products labeled for both adults and children."*

The agency has removed the warning concerning persistent cough as the sign of a serious condition from sections with specific labeling only for adults or only for children under 12 years of age and specified this warning in § 341.74(c)(1) as a general warning required for all antitussive drug products. The agency has revised the heading in § 341.74(c) for warnings for antitussives labeled for adults to read *"For oral and topical antitussives labeled for adults or for adults and children under 12 years of age"* to clarify that the warning "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor" is required for products labeled for both adults and children under 12 years of age as well as for adults only.

The agency has removed the warning concerning constipation for drug products containing codeine from sections that specify separate labeling for adults or for children under 12 years of age and specified this warning in § 341.74(c)(4)(i) as a general warning for all drug products containing codeine. To eliminate unnecessary repetition of information in the labeling of drug products containing codeine, the agency has revised and combined the warnings required for codeine products labeled for adults and children under 12 years of age that warn against use of such products in adults and children with a chronic pulmonary disease or shortness of breath or in children who are taking other drugs and included the revised warning in § 341.74(c)(4)(iv) of the monograph.

The agency has also deleted the warning "For external use only. Do not give by mouth or place in nostrils" for products containing camplor or menthol that was proposed for products labeled only for use in children under 12 years of age. The agency is requiring the warning "For external use only. Do not

take this by mouth or place in nostrils" that was proposed for products labeled only for adult use, for all products whether they are labeled only for adults, only for children under 12 years of age, or for adults and children under 12 years of age.

6. In order to assure that parents will obtain and use a calibrated measuring device when codeine products are used in children 2 to under 6 years of age, the agency is expanding that portion of § 341.74(d)(1)(ii) concerning children under 6 years of age to read: "Children under 6 years of age: Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could result in serious side effects for your child." (See comment 10 above.)

7. In order to clarify the professional labeling for products containing codeine, the agency is revising § 341.90(p)(2), redesignated as § 341.90(c)(2), to read: "Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not to exceed the recommended daily dosage" and is adding to § 341.90(p)(1), redesignated as § 341.90(c)(1), the statement "the manufacturer must relate these dosages for its specific product to the use of the calibrated measuring device discussed in paragraph (3) of this section." Also, § 341.90(p)(3), redesignated as § 341.90(c)(3), is revised to read "A dispensing device (such as a dropper calibrated for age and weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose." (See comment 10 above.) Furthermore, the agency is including a statement concerning the hazards of codeine use in children under 2 years of age under professional labeling in § 341.90(c)(4). (See comment 15 above.)

8. The agency is deleting the word "high" (in reference to fever) from the warning for antitussives proposed in § 341.74(c) (1)(ii) and (2)(ii) of the tentative final monograph. Fever can be defined as a body temperature above the normal temperature of 98.6 °F (37 °C). In the same or different disease states, however, fevers may vary significantly. Fever may be low grade, moderate, high, intermittent, or sustained. The particular characteristics of a fever depend on the disease state, and, in many cases, the stage of development of the disease. The word "high" has been deleted from the warning because the agency believes that it is important for the consumer to recognize the presence of fever regardless of whether the fever is high or low.

9. In order to clarify the dosage directions for dextromethorphan and dextromethorphan hydrobromide, the agency is adding the following statement to § 341.74(d)(1)(iii): The dosage is equivalent to dextromethorphan hydrobromide. The antitussive drug products containing dextromethorphan that were marketed at the time of the Panel's review contained the hydrobromide salt of this ingredient, and the dosages were based on this salt. The agency is unaware of any drug products that contained dextromethorphan at the time of the Panel's review. A compendial monograph for dextromethorphan did not become official until 1985 (Ref. 1).

Further, a sustained release drug product approved on October 8, 1982, under an NDA (Ref. 2) contained as its active ingredient dextromethorphan polistirex. The dosage for that product is equivalent to the dosage for dextromethorphan hydrobromide. To be consistent with the drug products reviewed by the Panel and approved by the agency under the NDA, the agency is clarifying that the dosages for drug products containing dextromethorphan be equivalent to the dosages for dextromethorphan hydrobromide.

References

(1) "The United States Pharmacopeia XXI—The National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 298–299, 1985.

(2) Letter from R. Temple, FDA, to L. Gundersen, Pennwalt Corporation, contained in OTC Volume 04TFM, Docket No. 76N–052T, Dockets Management Branch.

10. In a separate rulemaking, paragraph (b) of 21 CFR 1308.15 was redesignated as paragraph (c) (February 28, 1985; 50 FR 8104). Therefore, the agency has revised § 341.14(a)(2) by replacing the reference to paragraph (b) of § 1308.15 with a reference to paragraph (c) of § 1308.15.

11. The agency has redesignated § 341.3(j) as § 341.3(b) and § 341.90(o) as § 341.90(b).

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

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC antitussive drug products are generally recognized as safe and effective and not misbranded. Specifically, the following ingredients are included in this final rule for OTC antitussive use: chlophedianol hydrochloride, codeine ingredients (codeine, codeine phosphate, and codeine sulfate used only in combination in accordance with §§ 329.20 (a), 341.40, and 1308.15(c)), dextromethorphan, dextromethorphan hydrobromide, camphor, and menthol. All other ingredients for OTC antitussive use in this rulemaking are considered nonmonograph ingredients, i.e., beechwood creosite, benzonatate, camphor lozenges, caramiphen edisylate, carbetapentane citrate, cod liver oil, diphenhydramine hydrochloride, elm bark, ethylmorphine hydrochloride, eucalyptol/eucalyptus oil, horehound, hydrocodone bitartrate, menthol lozenges (less than 5 mg and greater than 10 mg), menthol mouthwash, noscapine, noscapine hydrochloride, thymol, and turpentine oil. Any drug product marketed for use as an OTC antitussive drug product that is not in conformance with the monograph (21 CFR Part 341) will be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and misbranded under section 502(a) of the act (21 U.S.C. 352(a)) and may not be marketed for this use unless it is the subject of an approved application.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (48 FR 48576). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this final rule for OTC antitussive drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular

rulemaking for OTC antitussive drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency is removing portions of § 369.20, § 369.21, and the exemption for certain drugs limited by NDAs to prescription sale in § 310.201(a)(14) applicable to dextromethorphan hydrobromide because these portions of those regulations are superseded by the requirements of the antitussive final monograph (Part 341). The items being removed include § 310.201(a)(14), the reference to paragraph (14) of § 310.201(a) in the entry for " 'COUGH-DUE-TO-COLD' PREPARATIONS" in § 369.20, and the term "DEXTROMETHORPHAN HYDROBROMIDE" as well as the reference to paragraph (14) of § 310.201(a) from the entry " 'COUGH-DUE-TO-COLD' PREPARATIONS (DEXTROMETHORPHAN HYDROBROMIDE AND CARBETAPENTANE CITRATE)" and by removing the entry "DEXTROMETHORPHAN HYDROBROMIDE PREPARATIONS" in § 369.21.

List of Subjects

21 CFR Part 310

New drugs, Prescription exemption.

21 CFR Part 341

Labeling, Over-the-counter drugs, Bronchodilator drug products.

21 CFR Part 369

OTC drugs, Warning and caution statements.

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

PART 310—NEW DRUGS

1. The authority citation for 21 CFR Part 310 is revised to read as follows:

Authority: Secs. 502, 503, 505, 701, 52 Stat. 1051, 1052, 1053, 1055 as amended (21 U.S.C. 352, 353, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

§ 310.201 [Amended]

2. In Subpart C, § 310.201 is amended by removing paragraph (a)(14) and reserving it for future use.

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 (established in the **Federal Register** of October 2, 1986; 51 FR 35326) is revised to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

4. In Subpart A, § 341.3 is amended by adding paragraphs (b) and (c), to read as follows:

§ 341.3 Definitions.

* * * * *

(b) *Oral antitussive drug.* A drug that is taken by mouth and acts systemically to relieve cough.

(c) *Topical antitussive drug.* A drug that relieves cough when inhaled after being applied topically to the throat or chest in the form of an ointment or from a steam vaporizer, or when dissolved in the mouth in the form of a lozenge or compressed tablet.

5. In Subpart B, § 341.14 is added, to read as follows:

§ 341.14 Antitussive active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient in § 341.74(d):

(a) *Oral antitussives.* (1) Chlophedianol hydrochloride.

(2) *Codeine ingredients.* The following ingredients may be used only in combination in accordance with §§ 329.20(a) and 341.40 and 21 CFR 1308.15(c).

(i) Codeine.

(ii) Codeine phosphate.

(iii) Codeine sulfate.

(3) Dextromethorphan.

(4) Dextromethorphan hydrobromide.

(b) *Topical antitussives.*

(1) Camphor.

(2) Menthol.

6. In Subpart C, § 341.74 is added, to read as follows:

§ 341.74 Labeling of antitussive 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 "cough suppressant" or an "antitussive (cough suppressant)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of 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) "Temporarily" (select one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough due to" (select one of the following: "minor bronchial irritation" or "minor throat and bronchial irritation") (select one of the following: "as may occur with," "associated with," or "occurring with") (select one of the following: "A cold" or "the common cold") "or inhaled irritants."

(2) "Temporarily" (select one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough" (select one of the following: "as may occur with," "associated with," or "occurring with") (select one of the following: "A cold," "the common cold," or "inhaled irritants").

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

(i) "Cough suppressant which temporarily" (select one of the following: "Alleviates," "controls," "decreases," "reduces," "relieves," or "suppresses") "the impulse to cough."

(ii) "Temporarily helps you cough less."

(iii) "Temporarily helps to" (select one of the following: "Alleviate," "control," "decrease," "reduce," "relieve," or "suppress") "the cough reflex that causes coughing."

(iv) "Temporarily" (select one of the following: "Alleviates," "controls," "decreases," "reduces," "relieves," or "suppresses") "the intensity of coughing."

(v) (Select one of the following: "Alleviates," "Controls," "Decreases," "Reduces," "Relieves," or "Suppresses") (select one of the following: "Cough," "the impulse to cough," or "your cough") "to help you" (select one of the following: "Get to sleep," "sleep," or "rest").

(vi) *For products containing chlophedianol hydrochloride, codeine ingredients, dextromethorphan, or dextromethorphan hydrobromide identified in § 341.14(a) (1), (2), (3), and*

(4). "Calms the cough control center and relieves coughing."

(vii) *For products containing chlophedianol hydrochloride, dextromethorphan, dextromethorphan hydrobromide, camphor, or menthol identified in § 341.14(a) (1), (3), (4) and (b) (1) and (2).* (*a*) "Nonnarcotic cough suppressant for the temporary" (select one of the following: "alleviation," "control," "decrease," "reduction," "relief," or "suppression") "of cough."

(*b*) (Select one of the following: "Alleviates," "Controls," "Decreases," "Reduces," "Relieves," or "Suppresses") "cough impulses without narcotics."

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

(1) *For oral and topical antitussives.* "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor."

(2) *For oral and topical antitussives labeled for adults or for adults and children under 12 years of age.* "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(3) *For oral and topical antitussives labeled only for children under 12 years of age.* "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

(4) *Oral antitussives*—(i) *For products containing codeine ingredients identified in § 341.14(a)(2).* "May cause or aggravate constipation."

(ii) *For products containing codeine ingredients identified in § 341.14(a)(2) when labeled only for adults.* "Do not take this product if you have a chronic pulmonary disease or shortness of breath unless directed by a doctor."

(iii) *For products containing codeine ingredients identified in § 341.14(a)(2) when labeled only for children under 12 years of age.* "Do not give this product to children who have a chronic pulmonary disease, shortness of breath, or who are taking other drugs unless directed by a doctor."

(v) *For products containing codeine ingredients identified in § 341.14(a)(2) when labeled for use in adults and children under 12 years of age.* "Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor."

(5) *Topical antitussives*—(i) *For products containing camphor or menthol identified in § 341.14(b) (1) and (2) in a suitable ointment vehicle.* "For external use only. Do not take by mouth or place in nostrils."

(ii) *For products containing camphor or menthol identified in § 341.14(b) (1) and (2) for steam inhalation use.* "For steam inhalation only. Do not take by mouth."

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

(1) *Oral antitussives*—(i) *For products containing chlophedianol hydrochloride identified in § 341.14(a)(1).* Adults: oral dosage is 25 milligrams every 6 to 8 hours, not to exceed 100 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

(ii) *For products containing codeine ingredients identified in § 341.14(a)(2).* Adults: Oral dosage is 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children under 6 years of age: Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could result in serious side effects for your child.

(iii) *For products containing dextromethorphan or dextromethorphan hydrobromide identified in § 341.14(a) (3) and (4).* The dosage is equivalent to dextromethorphan hydrobromide. Adults: Oral dosage is 10 to 20 milligrams every 4 hours or 30 milligrams every 6 to 8 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor. Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 hours or 15 milligrams every 6 to 8 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor. Children 2 to under 6 years of age: Oral dosage is 2.5 to 5 milligrams every 4 hours or 7.5 milligrams every 6 to 8 hours, not to exceed 30 milligrams in 24 hours, or as directed by a doctor. Children under 2 years of age: consult a doctor.

(2) *Topical antitussives*—(i) *For products containing camphor identified in § 341.14(b)(1) in a suitable ointment vehicle.* The product contains 4.7 to 5.3 percent camphor. Adults and children 2 to under 12 years of age: Rub on the throat and chest as a thick layer. The area of application may be covered with a warm, dry cloth if desired. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

(ii) *For products containing menthol identified in § 341.14(b)(2) in a suitable ointment vehicle.* The product contains 2.6 to 2.8 percent menthol. Adults and children 2 to under 12 years of age: Rub on the throat and chest as a thick layer. The area of application may be covered with a warm, dry cloth if desired. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

(iii) *For products containing menthol identified in § 341.14(b)(2) in a lozenge or compressed tablet.* The product contains 5 to 10 milligrams menthol. Adults and children 2 to under 12 years of age: Allow (lozenge or compressed tablet) to dissolve slowly in the mouth. May be repeated every hour as needed or as directed by a doctor. Children under 2 years of age: consult a doctor.

(iv) *For products containing camphor identified in § 341.14(b)(1) for steam inhalation use.* The product contains 6.2 percent camphor. Adults and children 2 to under 12 years of age: Add 1 tablespoonful of solution, for each quart of water, directly to the water in a hot steam vaporizer, bowl, or wash basin; or add 1½ teaspoonsful of solution, for each pint of water, to an open container of boiling water. Breathe in the medicated vapors. May be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

(v) *For products containing menthol identified in § 341.14(b)(2) for steam inhalation use.* The product contains 3.2 percent menthol. Adults and children 2 to under 12 years of age: Add 1 tablespoonful of solution, for each quart of water, directly to the water in a hot steam vaporizer, bowl, or wash basin; or add 1½ teaspoonsful of solution, for each pint of water, to an open container of boiling water. Breathe in the medicated vapors. May be repeated up to three times daily or as directed by a doctor. Children under 2 years of age: consult a doctor.

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

7. In Subpart C, § 341.90 is amended by adding paragraphs (b) and (c), to read as follows:

§ 341.90 Professional labeling.

* * * * *

(b) *For products containing chlophedianol hydrochloride identified in 341.14(a)(1).* Children 2 to under 6 years of age: oral dosage is 12.5 milligrams every 6 to 8 hours, not to exceed 50 milligrams in 24 hours.

(c) *For products containing codeine ingredients identified in § 341.14(a)(2).* (1) Children 2 to under 6 years of age: Oral dosage is 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows: For children 2 years of age (average body weight, 12 kilograms), the oral dosage is 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours; for children 3 years of age (average body weight, 14 kilograms), the oral dosage is 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours; for children 4 years of age (average body weight, 16 kilograms), the oral dosage is 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours: for children 5 years of age (average body weight, 18 kilograms), the oral dosage is 4.5 milligrams every 4 to 6 hours, not to exceed 18 milligrams in 24 hours. The manufacturer must relate these dosages for its specific product dosages for its specific product to the use of the calibrated measuring device discussed in paragraph (c)(3) of this section. If age is used to determine the dose, the directions must include instructions to reduce the dose for low-weight children.

(2) Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not exceed the recommended daily dosage.

(3) A dispensing device (such as a dropper calibrated for age or weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose.

(4) Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death.

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

8. The authority citation for 21 CFR Part 369 is revised to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050–1052 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

§ 369.20 [Amended]

9. In Part 369, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the reference to paragraph (14) of § 310.201(a) from the entry " 'COUGH-DUE-TO-COLD' PREPARATIONS."

§ 369.21 [Amended]

10. In Part 369, § *369.21 Drugs; warning and caution statements required by regulations* is amended by removing the term "DEXTROMETHORPHAN HYDROBROMIDE" and by removing the reference to paragraph (14) of § 310.201(a) from the entry " 'COUGH-DUE-TO-COLD' PREPARATIONS (DEXTROMETHORPHAN HYDROBROMIDE AND CARBETAPENTANE CITRATE) and by removing the entry "DEXTROMETHORPHAN HYDROBROMIDE PREPARATIONS."

Dated: May 2, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 87–18144 Filed 8–11–87; 8:45 am]

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federal register

Wednesday
August 12, 1987

Part IV

Department of Education

34 CFR 350, 351, 352, 353, 354, 355, 356, 357, 358, and 359

National Institute on Disability and Rehabilitation Research; Final Regulations and Notice of Final Funding Priorities for Fiscal Year 1987

DEPARTMENT OF EDUCATION

34 CFR Parts 350, 351, 352, 353, 354, 355, 356, 357, 358, and 359

National Institute on Disability and Rehabilitation Research

AGENCY: Department of Education.

ACTION: Final regulations.

SUMMARY: The Secretary amends the regulations governing the National Institute on Disability and Rehabilitation Research (NIDRR). These regulations implement certain changes to Titles I and II of the Rehabilitation Act of 1973 made by the Rehabilitation Act Amendments of 1986. The regulations revise the selection criteria for Rehabilitation Research and Training Centers (RRTC's) and Rehabilitation Engineering Centers (REC's) supported by NIDRR, incorporate site visits into the review of applications for grants for amounts above $299,999, provide for the consideration of an applicant's past performance in the evaluation of applications under the RRTC and REC programs, and incorporate certain technical requirements of the amendments.

EFFECTIVE DATE: These regulations take effect either 45 days after publication in the **Federal Register** or later if the Congress takes certain adjournments. If you want to know the effective date of these regulations, call or write the Department of Education contact person.

FOR FURTHER INFORMATION CONTACT: Betty Jo Berland, National Institute on Disability and Rehabilitation Research, 400 Maryland Avenue SW., Washington, DC, 20202. Telephone (202) 732-1142; deaf or hearing impaired persons who use telecommunication devices for the deaf (TDD) may call (202) 732-1198.

SUPPLEMENTARY INFORMATION: The National Institute on Disability and Rehabilitation Research (NIDRR), created under Title II of the Rehabilitation Act of 1973, as amended by Public Laws 95-602, 98-221, and 99-506, carries out a variety of research and related activities under that statutory authority. On September 10, 1981, the Secretary published final program regulations governing many of those activities (46 FR 45300), and on March 12, 1984, June 18, 1984, and April 26, 1985, revised those regulations (49 FR 9324 and 24978, and 50 FR 16672). The Secretary now amends the regulations to implement changes to the Act affecting NIDRR made by Pub. L. 99-506, the Rehabilitation Act Amendments of 1986, enacted on October 21, 1986. The 1986 amendments made a number of technical changes in the authority governing NIDRR and several significant changes affecting the manner in which applications are reviewed and selected for funding. These revised regulations incorporate the technical changes and also provide new selection criteria for two programs, as well as certain new peer review requirements.

On May 7, 1987, the Secretary published a notice of proposed rulemaking for NIDRR at 52 FR 17368. NIDRR received a number of comments, and several changes have been made to the proposed regulations in response to those comments. A Summary of the Comments and Responses is included as an Appendix to this document. The principal changes are an increase in the number of points awarded to the quality of the research design in the evaluation of applications for Rehabilitation Research and Training Centers (RRTC's), and a concomitant decrease in the maximum number of points awarded for two other selection criteria, relevance and importance of the research program and quality of the organization and management. However, these changes will not become effective until fiscal year 1988, as there was not sufficient time for NIDRR to make these changes effective for 1987 and still fund the Centers for which the Congress has directed funding.

Other changes from the proposed regulations are primarily to clarify the intent of the regulations. These include inserting physical restoration as one of the problem areas to be addressed by NIDRR-supported research; expanding references to rehabilitation of children with handicaps to include infants, toddlers, children, and youth; specifying that peer reviewers must have expertise related to the specific applications under review; including communication factors as subjects of the Research and Demonstration projects program (§ 351.10); and clarifying the requirement that Centers prepare materials in alternate media accessible to individuals with various types of disabilities.

Executive Order 12291

These regulations have been reviewed in accordance with Executive Order 12291. They are not classified as major because they do not meet the criteria for major regulations specified in the order.

Assessment of Educational Impact

In the notice of proposed rulemaking, the Secretary requested comments on whether the proposed regulations would require transmission of information that is being gathered by or is available from any other agency or authority in the United States. Based on the response to the proposed rules and on its own review, the Department has determined that the regulations in this document do not require transmission of information that is being gathered by or is available from any other agency or authority of the United States.

List of Subjects

34 CFR Part 350

Administrative practice and procedure, Education, Educational research, Grant programs—education, Handicapped.

34 CFR Parts 351 and 353

Grant programs—education, Research, Vocational rehabilitation.

34 CFR Part 352

Education, Educational research, Grant programs—education, Handicapped, Manpower training programs, Vocational rehabilitation.

34 CFR Part 359

Education, Educational research, Grant programs—education, Handicapped, Vocational rehabilitation.

(Catalog of Federal Domestic Assistance Number 84.133, National Institute on Disability and Rehabilitation Research)

Dated: July 23, 1987.

William J. Bennett,

Secretary of Education.

The Secretary amends Title 34 of the Code of Federal Regulations by amending Parts 350, 351, 352, 353, 354, 355, 356, 357, 358, and 359 as follows:

PART 350—[AMENDED]

1. The authority citation for Part 350 is revised to read as follows:

Authority: 29 U.S.C. 760-762, unless otherwise noted.

2. The title of Part 350 is revised to read as follows:

PART 350—DISABILITY AND REHABILITATION RESEARCH: GENERAL PROVISIONS

3. In § 350.1, the introductory text of (a) is republished, and the section is amended by revising the section heading, paragraphs (a) (1) and (3), and the citation of legal authority to read as follows:

§ 350.1 Disability and rehabilitation research.

(a) The purposes of activities funded by the Institute are to:

(1) Support the conduct of research and demonstration projects, centers, and related activities that address rehabilitation problems in areas such as physical restoration, vocational rehabilitation, independent living, and community integration for persons with handicaps, including programs of rehabilitation for infants, toddlers, children, and youth with handicaps and persons with handicaps aged sixty or older (fifty-five or older in the case of American Indians), and programs that train persons who provide rehabilitation services or conduct research;

* * * * *

(3) Improve the distribution of technological devices and equipment for persons with handicaps; and

* * * * *

(Authority: Secs. 200, 202, and 204; (29 U.S.C. 760, 761a, and 762))

4. Section 350.2 is amended by revising paragraphs (b) and (c), adding a new paragraph (d), and revising the citation of legal authority to read as follows:

§ 350.2 Who is eligible for assistance under these programs?

* * * * *

(b) Private agencies or organizations;

(c) Institutions of higher education; and

(d) Indian tribes and tribal organizations.

(Authority: Sec. 204(a); 29 U.S.C. 762a)

5. Section 350.3 is amended by revising the introductory text and paragraph (a)(2) to read as follows:

§ 350.3 What regulations apply to these programs?

The following regulations apply to grants under the Disability and Rehabilitation Research Programs—

(a) * * *

(2) Part 75 (Direct Grant Programs), except as noted in 34 CFR 352.33, 352.40, and 358.3;

* * * * *

6. Section 350.4 is amended by revising the introductory text in paragraphs (a) and (b); and also in paragraph (b) by removing the definitions of "Director" and "Handicapped individual" and their corresponding citations of legal authority, by revising the definition of "Institute", and adding new definitions of "American Indian", "Indian tribe", "Individual with handicaps", "Individual with severe handicaps", "Rehabilitation engineering", and "Supported employment", to read as follows:

§ 350.4 What definitions apply to these programs?

(a) The following definitions in 34 CFR Part 77 apply to the programs under Disability and Rehabilitation Research—

* * * * *

(b) The following definitions also apply to programs under Disability and Rehabilitation Research—

* * * * *

"American Indian" means an individual who is a member of an Indian tribe.

(Authority: Sec. 7(20); 29 U.S.C. 706(20))

* * * * *

"Indian tribe" means any Federal or State Indian tribe, band, rancheria, pueblo, colony, or community, including any Alaskan native village or regional village corporation, as defined in or established pursuant to the Alaska Native Claims Settlement Act.

(Authority: Sec. 7(21); 29 U.S.C. 706(21))

"Individual with handicaps" means any individual who: (1) Has a physical or mental disability which for that individual constitutes or results in a substantial handicap to employment; and (2) can reasonably be expected to benefit in terms of employability from the provision of vocational rehabilitation services.

(Authority: Sec 7(8)(A); 29 U.S.C. 706(8)(A))

"Individual with severe handicaps" means an individual with handicaps: (1) Who has a severe physical or mental disability that seriously limits one or more functional capacities (such as mobility, communication, self-care, self-direction, interpersonal skills, work tolerance, or work skills) in terms of employability; (2) whose vocational rehabilitation can be expected to require multiple vocational rehabilitation services over an extended period of time; and (3) who has one or more physical or mental disabilities resulting from amputation, arthritis, autism, blindness, burn injury, cancer, cerebral palsy, cystic fibrosis, deafness, head injury, heart disease, hemiplegia, hemophilia, respiratory or pulmonary dysfunction, mental retardation, mental illness, multiple sclerosis, muscular dystrophy, musculoskeletal disorders, neurological disorders (including stroke and epilepsy), paraplegia, quadriplegia, other spinal cord conditions, sickle cell anemia, specific learning disability, endstage renal disease, or another disability or combination of disabilities determined on the basis of an evaluation of rehabilitation potential to cause comparable substantial functional limitation.

(Authority: Sec. 7(15)(A); 29 U.S.C. 706(15)(A))

"Institute" means the National Institute on Disability and Rehabilitation Research.

* * * * *

"Rehabilitation engineering" means the systematic application of technologies, engineering methodologies, or scientific principles to meet the needs of an address the barriers confronted by individuals with handicaps in areas that include education, rehabilitation, employment, transportation, independent living, and recreation.

(Authority: Sec. 7(12); 29 U.S.C. 706(12))

* * * * *

"Supported employment" means competitive work in integrated work settings for individuals with severe handicaps for whom competitive employment has not traditionally occurred, or for whom competitive employment has been interrupted or intermittent as a result of severe disability, and who, because of the handicaps, need on-going support services to perform that work. The term includes transitional employment for individuals with chronic mental illness.

(Authority: Sec. 7(18); 29 U.S.C. 706(18))

* * * * *

7. Section 350.30 is revised to read as follows:

§ 350.30 What are the peer review panels for these programs?

The Secretary refers each application for a grant under the Disability and Rehabilitation Research Programs to a peer review panel established by the Secretary. Peer review panels review applications on the basis of the applicable selection criteria described in 34 CFR 350.34, 352.31, 353.31, 358.32, or 359.31.

(Authority: Sec. 202(e); 29 U.S.C. 761a(e))

8. Section 350.32 is amended by revising paragraph (a) and the citation of legal authority to read as follows:

§ 350.32 What is the composition of a peer review panel?

(a) The Secretary selects as members of a peer review panel scientists and other experts in rehabilitation or related fields who are qualified, on the basis of training, knowledge, or experience, to give expert advice on the merit of the applications under review. Applications for awards of $60,000 or more, except those for the purposes of evaluation, dissemination of information, or conferences, must be reviewed by a peer

review panel that consists of a majority of non-Federal members.

* * * * *

(Authority: Secs. 18 and 202(e); 29 U.S.C. 717 and 761a(e))

9. Section 350.33 is amended by revising paragraphs (a), (b), and (e) and the first sentence of paragraph (c) to read as follows:

§ 350.33 How does the Secretary evaluate an application under 34 CFR Parts 351, 354, 355, or 357?

(a) The Secretary evaluates an application under 34 CFR Part 351, 354, 355, or 357 on the basis of the selection criteria in § 350.34.

(b) Each criterion applies to all types of projects under the programs governed by these parts; the elements within each criterion also apply to all of the activities within the projects unless the regulations specifically state that their application is limited to certain types of activities.

(c) The Secretary awards up to five possible points for each criterion. * * *

* * * * *

(e) The maximum possible score for an application is 100 points.

(Authority: Sec. 202(e); 29 U.S.C. 761a(e))

10. The heading of § 350.34 is revised to read as follows:

§ 350.34 What selection criteria does the Secretary use in reviewing applications under Parts 351, 354, 355, or 357?

* * * * *

11. In Subpart D, a new § 350.35 is added to read as follows:

§ 350.35 What additional factors does the Secretary consider in reviewing applications under any Institute program:

(a) In making grants of more than $299,999 per year under any Institute program, the Secretary also considers the findings of an on-site review of the applicant. An on-site review is made of the applicant rated most highly by the peer review panel, and, at the discretion of the Secretary, of other applicants that are very highly rated by the peer review panel.

(b) The purpose of an on-site review is to verify certain aspects of the application, including facilites and resources, client populations, staffing, management structure, institutional support, and relations with other agencies, and to clarify certain aspects of the proposed activity if recommended by the members of the peer review panel.

(c) An on-site review is conducted by a group that includes one or more members of the peer review panel that originally reviewed by the application, supplemented by other experts as necessary.

(d) The Secretary uses the findings of the site review to assist in determining the order in which applications are selected for funding.

(Authority: Secs. 204(d)(2); 29 U.S.C. 762(d))

12. In § 350.40, the introductory text of (b)(1) is republished, and the section is amended by revising paragraph (b)(1)(iii) to read as follows:

§ 350.40 What are the matching requirements?

* * * * *

(b)(1) The Secretary may make grants to pay for part or all of the costs of the following activities:

* * * * *

(iii) Research projects concerned with end-stage renal disease, telecommunications, rehabilitation of children with handicaps and persons with handicaps who are aged sixty or older (or American Indians with handicaps who are aged fifty-five or older), attracting and retaining rehabilitation professionals in rural areas, producing and distributing captioned video cassettes for deaf individuals and innovative methods for providing services for children with handicaps and their parents.

* * * * *

PART 351—[AMENDED]

13. The authority citation for Part 351 is revised to read as follows:

Authority: 29 U.S.C. 750–762, unless otherwise noted.

14. The title of Part 351 is revised to read as follows:

PART 351—DISABILITY AND REHABILITATION RESEARCH: RESEARCH AND DEMONSTRATION PROJECTS

§ 351.1 [Amended]

§ 351.10 [Amended]

15. In Part 351, for each section listed in the left column in the list below, remove the phrase in the middle column from wherever it appears in the section, and add the phrase indicated in the right column in its place:

Sec.	Remove	Add
351.1	"handicapped individual", "handicapped individuals", "the most severely handicapped"	"individual with handicaps" "individuals with handicaps" "individuals with the most severe handicaps"
351.10	"handicapped individual"	"individual with handicaps"
	"handicapped individuals" "handicapped children"	"individuals with handicaps" "children with handicaps"
	"handicapped preschool children"	"children of preschool age with handicaps"
	"handicapped individuals aged sixty years and older"	"individuals with handicaps who are aged sixty years and older, or, in the case of American Indians, are aged fifty-five years or older"

16. In § 351.10 the introductory text of the section and the introductory text of paragraph (b) are republished, and the section is amended by revising paragraph (a), revising paragraphs (b)(6) and (7), and the citation of legal authority and adding new paragraphs (b)(8) and (9) to read as follows:

§ 351.10 What types of projects are authorized under this program?

The Research and Demonstration Projects Program provides financial assistance for the following types of projects—

(a) Research and Demonstration Projects as follows—Scientific, technical, methodological, and other investigations into the nature of disability, methods of analyzing disability, and techniques for rehabilitation, including basic research where related to rehabilitation techniques or services; studies and analyses of medical, industrial, vocational, social, recreational, psychiatric, psychological, communicative, economic, and other factors affecting rehabilitation of individuals with handicaps; research concerned with the special problems of homebound and institutionalized individuals; other research related to problems encountered by individuals with handicaps in their daily activities, especially problems related to employment, including supported employment; and demographic studies of individuals with handicaps.

(b) Specialized research activities as follows—

* * * * *

(6) Projects to develop and demonstrate methods to attract and retain professionals to serve in rural areas in the rehabilitation of individuals with handicaps;

(7) Research and demonstration projects related to the provision of services to children of preschool age with handicaps;

(8) Studies of the rehabilitation needs of American Indian populations, and of effective means for delivery of rehabilitation services to American

Indians residing on and off reservations; and

(9) Studies and demonstration programs to develop procedures to encourage development, manufacture, and marketing or orphan technological devices, such as tele-Braille systems for persons who are deaf-blind or special respirators for technology-dependent children, designed to enable individuals with handicaps to achieve independence and access to gainful employment.

(Authority: 204(a), 204(b)(3)–(5), 204(b)(7)–(9), 204(b)(11), 204(b)(14)–(15), and 202(b)(8); 29 U.S.C. 762(a), 762(b)(3)–(5), 762(b)(7)–(9), 762(b)(11), 762(b)(14)–(15), and 761a(b)(8))

PART 352—[AMENDED]

17. The authority citation for Part 352 is revised to read as follows:

Authority: 29 U.S.C. 762(b)(1), unless otherwise noted.

18. The title of Part 352 is revised to read as follows:

PART 352—DISABILITY AND REHABILITATION RESEARCH: REHABILITATION RESEARCH AND TRAINING CENTERS

19. Section 352.10 is amended by revising paragraphs (b) and (d) to read as follows:

§ 352.10 What types of centers are authorized under this program?

* * * * *

(b) The research to be conducted at each center must be based on the particular needs of individuals with handicaps in the geographic area served by the center. Centers may conduct basic research, if related to identifiable rehabilitation techniques or services, as well as applied rehabilitation research; research regarding the medical, psychological, and social aspects of rehabilitation; and research related to vocational rehabilitation, independent living, and the rehabilitation of infants, toddlers, children, and youth with handicaps, individuals with handicaps who are sixty years of age or older, or American Indians with handicaps who are fifty-five years of age or older; and research on problems related to disability in rural areas.

* * * * *

(d) A center may use part of its grant funds to provide to individuals with handicaps services that are connected with its research and training activities.

(Authority: Sec. 204(b)(1); 29 U.S.C. 762(b)(1))

20. Section 352.31 is revised to read as follows:

§ 352.31 What selection criteria are used under this program?

The Secretary evaluates applications under this program according to the following criteria:

(a) *Relevance and importance of the research program.* (20 points)

(Note.—For fiscal year 1987 only, the maximum number of points to be awarded under this criterion is 25 points.)

The Secretary reviews each application to determine to what degree—

(1) The proposed activities are responsive to a priority established by the Secretary and address a significant need of a disabled target population and rehabilitation service providers;

(2) The overall research program of the Center includes appropriate interdisciplinary and collaborative research activities, is likely to lead to new and useful knowledge in the priority area, and is likely to become a nationally recognized source of scientific knowledge; and

(3) The applicant demonstrates that all component activities of the Center are related to the overall objective of the Center, and will build upon and complement each other to enhance the likelihood of solving significant rehabilitation problems.

(b) *Quality of the research design.* (35 points)

(Note.—For fiscal year 1987 only, the maximum number of points to be awarded under this criterion is 25 points.)

The Secretary reviews each application to determine to what degree—

(1) The applicant proposes a comprehensive research program for the entire project period, including at least three interrelated research projects;

(2) The research design and methodology of each proposed activity are meritorious in that—

(i) The literature review is appropriate and indicates familiarity with current research in the field;

(ii) The research hypotheses are important and scientifically relevant;

(iii) The sample populations are appropriate and significant;

(iv) The data collection and measurement techniques are appropriate and likely to be effective;

(v) The data analysis methods are appropriate; and

(vi) The applicant assures that human subjects, animals, and the environment are adequately protected; and

(3) The application discusses the anticipated research results and demonstrates how those results would satisfy the original hypotheses and could be used for planning future research, including generation of new hypotheses where applicable.

(c) *Quality of the training and dissemination program.* (25 points): The Secretary reviews each application to determine the degree to which—

(1) The proposed plan for training and dissemination provides evidence that research results will be effectively disseminated and utilized based on the identification of appropriate and accessible target groups; the proposed training materials and methods are appropriate; the proposed activities are relevant to the regional and national needs of the rehabilitation field; and the training materials and dissemination packages will be developed in alternate media that are usable by people with various types of disabilities;

(2) The proposed plan for training and dissemination provides for—

(i) Advanced training in rehabilitation research;

(ii) Training rehabilitation service personnel and other appropriate individuals to improve practitioner skills based on new knowledge derived from research;

(iii) Training packages that make research results available to service providers, researchers, educators, disabled individuals, parents, and others;

(iv) Technical assistance or consultation that is responsive to the concerns of service providers and consumers; and

(v) Dissemination of research findings through publication in professional journals, textbooks, and consumer and other publications, and through other appropriate media such as audiovisual materials and telecommunications.

(d) *Quality of the organization and management.* (20 points):

(Note.—For fiscal year 1987 only, the maximum number of points to be awarded under this criterion is 25 points.)

The Secretary reviews each application to determine the degree to which—

(1) The staffing plan for the Center provides evidence that the project director, research director, training director, principal investigator and other personnel have appropriate training and experience in disciplines required to conduct the proposed activities; the commitment of staff time is adequate to conduct all proposed activities; and the Center, as part of its nondiscriminatory employment practices, will ensure that its personnel are selected for employment without regard to race, color, national origin, gender, age, or handicapping condition.

(2) The budgets for the Center and for each component project are reasonable, adequate, and cost-effective for the proposed activities;

(3) The facilities, equipment, and other resources are adequate and are appropriately accessible to persons with disabilities;

(4) The plan of operations is adequate to accomplish the Center's objectives and to ensure proper and efficient management of the Center;

(5) The proposed relationships with Federal, State, and local rehabilitation service providers and consumer organizations are likely to ensure that the Center program is relevant and applicable to the needs of consumers and service providers;

(6) The past performance and accomplishments of the applicant indicate an ability to complete successfully the proposed scope of work;

(7) The application demonstrates appropriate commitment and support by the host institution and opportunities for interdisciplinary activities and collaboration with other institutions and organizations; and

(8) The plan for evaluation of the Center provides for an annual assessment of the outcomes of the research, the impact of the training and dissemination activities on the target populations, and the extent to which the overall objectives have been accomplished.

(Authority: Secs. 202(e), 202(i)(1), and 204(b)(1); 29 U.S.C. 761a(e), 761a(i)(1)), and 762(b)(1))

(Approved by the Office of Management and Budget under control number 1820-0027.)

21. A new Subpart E, consisting of § 352.40, is added to read as follows:

Subpart E—What Conditions Apply to a Grantee?

§ 352.40 What are the indirect cost requirements for this program?

A host institution with which a center is affiliated may not collect in excess of fifteen percent of the total grant award as indirect cost charges, notwithstanding the provisions in § 75.562 of EDGAR.

(Authority: Sec. 204(b)(1); (29 U.S.C. 762(b)(1))

PART 353—[AMENDED]

22. The authority citation for Part 353 is revised to read as follows:

Authority: 29 U.S.C. 762(b)(2), unless otherwise noted.

23. The title of Part 353 is revised to read as follows:

PART 353—DISABILITY AND REHABILITATION RESEARCH: REHABILITATION ENGINEERING CENTERS

24. Section 353.1 is amended by revising paragraphs (b) and (c) to read as follows:

§ 353.1 What is the rehabilitation engineering program?

* * * * *

(b) Development of systems of technical and engineering information exchange and coordination, including systems to disseminate innovative methods for the delivery of rehabilitation technology services; and

(c) Development of improvements in the distribution of technology devices and equipment to individuals with handicaps.

(Authority: Secs. 200(3), 204(b)(2); 29 U.S.C. 760(3), 762(b)(2)).

25. In § 353.10, the introductory texts of (a) and (b) are republished, and the section is amended by removing the word "and" at the end of paragraph (a)(iii), removing the period at the end of paragraph (a)(iv) and adding, in its place, a semicolon and the word "and", adding a new paragraph (a)(v), and revising paragraph (b)(1), to read as follows:

§ 353.10 What types of projects are authorized under this program?

* * * * *

(a) Establishment and support of Rehabilitation Engineering Research Centers.

* * * * *

(v) The activities of a Center may include developing and demonstrating innovative models for the delivery to rural and urban areas of cost-effective rehabilitation engineering services to address the barriers to employment and independent living needs confronted by individuals with handicaps.

(b) Research and demonstration projects of an engineering or technolgical nature as follows—

(1) Studies, analyses, and demonstrations of architectural and engineering design adapted to meet the special needs of individuals with handicaps, and projects to reduce environmental barriers;

* * * * *

26. Section 353.31 is revised to read as follows:

§ 353.31 What selection criteria are used under this program?

(a) *Relevance and importance of the research program.* (25 points) The Secretary reviews each application to determine to what degree—

(1) The proposed activities are responsive to a priority established by the Secretary and address a significant need of a disabled target population and rehabilitation service providers;

(2) The overall research program of the Center includes appropriate interdisciplinary and collaborative research activities, is likely to lead to new and useful knowledge in the priority area and to the development of new technology or new applications of existing technology, and is likely to become a nationally recognized source of information on technology in the priority area; and

(3) The applicant demonstrates that all component activities of the Center are related to the overall objectives of the Center, and will build upon and complement each other to enhance the likelihood of finding solutions to significant rehabilitation problems.

(b) *Quality of the research design.* (25 points) The Secretary reviews each application to determine to what degree—

(1) The applicant proposes a comprehensive program of research for the total project period, including at least three interrelated research projects;

(2) The research design and methodology of each proposed activity are meritorious in that—

(i) The literature review is appropriate and indicates familiarity with the state-of-the-art and current research in rehabilitation technology;

(ii) The research hypotheses are important and scientifically relevant;

(iii) The sample populations are appropriate and significant;

(iv) The data collection and measurement techniques are appropriate and likely to be effective;

(v) The data analysis methods are appropriate; and

(vi) The applicant assures that human subjects, animals, and the environment are adequately protected:

(3) The plan for development, clinical testing, and evaluation of new devices and technology is likely to yield significant products; and

(4) The application discusses the anticipated research results and demonstrates how those results would satisfy the original hypotheses and could be used for planning additional research, including the generation of new hypotheses where applicable.

(c) *Quality of the dissemination and utilization program.* (25 points) The Secretary reviews each application to determine the degree to which—

(1) The proposed plan for dissemination provides evidence that

research results will be effectively disseminated and utilized based on the identification of appropriate and accessible target groups; the proposed activities are relevant to the regional and national needs of the rehabilitation field; and dissemination packages will be prepared in a form usable by individuals with all types of disabilities;

(2) The proposed plan for dissemination and utilization of the research and development provides for—

(i) Orientation programs for rehabilitation service personnel to improve the application of rehabilitation technology;

(ii) Programs which specifically demonstrate means for utilizing rehabilitation technology;

(iii) Technical assistance and consultation that are responsive to concerns of service providers and consumers; and

(iv) Dissemination of reseach findings through publication in professional journals, textbooks, and consumer and other publications, and through other appropriate media such as audiovisual materials and telecommunications, in an effort to make research results accessible to manufacturers, rehabilitation service providers, researchers, educators, disabled individuals and their families, and others; and

(3) There is an appropriate plan to ensure the distribution and utilization of new devices and technology.

(d) *Quality of the organization and management.* (25 points): The Secretary reviews each application to determine the degree to which—

(1) The staffing plan for the Center provides evidence that the principal investigator and other personnel have appropriate training and experience in disciplines required to conduct the proposed activities; the commitment of time for all staff is adequate to conduct all proposed activities; and the Center, as part of its nondiscriminatory employment practices, will ensure that its personnel are selected for employment without regard to race, color, national origin, gender, age, or handicapping condition;

(2) The budgets for the Center and each of the proposed activities are reasonable, adequate, and cost-effective for the proposed activities;

(3) The facilities, equipment, and other resources are adequate and are appropriately accessible to persons with disabilities;

(4) The plan of operations is adequate to accomplish the Center's objectives and to ensure proper and efficient management of the Center;

(5) The proposed relationships with Federal, State, and local rehabilitation service providers and consumer organizations are likely to ensure that the Center program is relevant and applicable to the needs of consumers and service providers;

(6) The past performance and accomplishments of the applicant indicate an ability to complete successfully the proposed scope of work;

(7) The application demonstrates appropriate commitment and support by the host institution and opportunities for interdisciplinary activities and collaboration with other institutions; and

(8) The plan for evaluation of the Center will assess annually the outcomes of the discrete and interrelated research projects, the impact of the training and dissemination activities on the target populations, and the extent to which the overall objectives have been accomplished.

(**Authority:** Secs. 202(e), 202(i)(1), and 204(b)(2); 29 U.S.C. 761a(e), 761a(i)(1), and 762(b)(2))

(Approved by the Office of Management and Budget under control number 1820–0027.)

PART 354—[AMENDED]

27. The citation of authority for Part 354 is revised to read as follows:

Authority: 29 U.S.C. 762(b)(12), unless otherwise noted.

28. The title of Part 354 is revised to read as follows:

PART 354—DISABILITY AND REHABILITATION RESEARCH: MODEL RESEARCH AND TRAINING PROGRAM

PART 355—[AMENDED]

29. The citation of authority for Part 355 is revised to read as follows:

Authority: 29 U.S.C. 760–762, unless otherwise noted.

30. The title of Part 355 is revised to read as follows:

PART 355—DISABILITY AND REHABILITATION RESEARCH: KNOWLEDGE DISSEMINATION AND UTILIZATION PROGRAMS

PART 356—[AMENDED]

31. The citation of authority for Part 356 is revised to read as follows:

Authority: 29 U.S.C. 761a(d), unless otherwise noted.

32. The title of Part 356 is revised to read as follows:

PART 356—DISABILITY AND REHABILITATION RESEARCH: RESEARCH FELLOWSHIPS

§ 356.30 [Amended]

§ 356.32 [Amended]

33. Part 356 is amended in the sections listed in the left column by removing the name in the middle column and adding in its place the name in the right column, as follows:

Sec.	Remove	Add
356.30(b)(1)	"NIHR"	"the Institute"
356.32(b)	"NIHR"	"Institute's"

PART 357—[AMENDED]

34. The citation of authority for Part 357 is revised to read as follows:

Authority: 29 U.S.C. 760–762, unless otherwise noted.

35. The title of Part 357 is revised to read as follows:

PART 357—DISABILITY AND REHABILITATION RESEARCH: FIELD-INITIATED RESEARCH PROJECTS

§ 357.1 [Amended]

36. In § 357.1, in each paragraph indicated in the left column, remove the name in the middle column and add in its place the name in the right column, as follows:

Sec.	Remove	Add
357.1 (b)	"NIHR"	"Institute"
357.1 (c)	"NIHR"	"Institute"

PART 358—[AMENDED]

37. The citation of authority for Part 358 is revised to read as follows:

Authority: 29 U.S.C. 762(b)(13), unless otherwise noted.

38. The title of Part 358 is revised to read as follows:

PART 358—DISABILITY AND REHABILITATION RESEARCH: INNOVATION GRANTS PROGRAM

PART 359—[AMENDED]

39. The citation of authority for Part 359 is revised to read as follows:

Authority: 29 U.S.C. 777a(a), unless otherwise noted.

40. The title of Part 359 is revised to read as follows:

PART 359—DISABILITY AND REHABILITATION RESEARCH—SPECIAL PROJECTS AND DEMONSTRATIONS FOR SPINAL CORD INJURIES

41. A new § 359.32 is added to Subpart D to read as follows:

§ 359.32 What additional factors does the Secretary consider in making a grant under this program?

In determining which applicants to fund under this program, the Secretary also considers the proposed location of any project in order to achieve, to the extent possible, a geographic distribution of projects.

(Authority: Section 204(b)(3) of the Rehabilitation Act of 1973, as amended; (29 U.S.C. 762(b)(3))

Editorial note: This appendix will not appear in the Code of Federal Regulations.

Appendix—Summary of Comments and Responses

NIDRR received several letters commenting on the proposed rules. A summary of those comments, and the Secretary's responses to them, follows.

Comment: Several commenters urged that NIDRR increase the relative weight assigned to the selection criterion "Quality of the research design" in the evaluation of applications for RRTC's (§ 352.31(b)).

Response: A change has been made. The Secretary has increased the maximum number of points assigned to that criterion from 25 to 35 points. This increase will demonstrate the primacy of the research program in an RRTC without neglecting the other elements of a Center. This change will take effect in fiscal year 1988, so that the fiscal year 1987 competitions that were announced under the Notice of Proposed Rulemaking will be evaluated under the criteria in the NPRM, which assign a maximum of 25 points to that criterion. This change was not made effective for fiscal year 1987 because NIDRR would not have time to notify all applicants, allow them an extension of time to amend or resubmit their applications, and still make the 1987 awards directed by the Congress.

Comment: Several commenters urged that in evaluating applications for Centers, past performance should not be interpreted to give preference to existing RRTC's, expecially if they are applying to be Centers in new priority areas.

Response: No change has been made. The selection criteria apply the standard "the past performance and accomplishments of the applicant indicate an ability to complete successfully the proposed scope of work" to all applicants for RRTC's and REC's, whether or not they have previously held NIDRR Center grants. Each applicant institution thus has an opportunity to describe and document those prior activities that indicate such an ability.

Comment: Several commenters requested that NIDRR make changes in the definitions of "rehabilitation engineering" and "supported employment."

Response: No change has been made. These definitions are provided in the legislation that governs NIDRR, the Rehabilitation Act of 1973, as amended.

Comment: One commenter suggested that references to "children with handicaps" in certain sections be changed to "infants, toddlers, children, and youth with handicaps" to be consistent with nomenclature in related programs.

Response: A change has been made. The Secretary has adopted this wording in the relevant sections of the regulations.

Comment: One commenter suggested that the description of the qualifications of peer reviewers (§ 350.32(a)) should stress that their expertise is in the content area of the applications under review.

Response: A change has been made. The proposed regulations have been amended to make it clear that the members of the peer review panel must have qualifications related to the specific applications under review.

Comment: One commenter suggested that applicants for Centers who may have had poor past records but have corrected the problems be permitted to appeal adverse evaluations or to explain the corrective actions they have taken.

Response: No change has been made. The selection criterion dealing with past performance is only one factor in evaluating an applicant. The applicant is permitted to submit any relevant documentation of institutional and staff capability, including evidence of corrective action.

Comment: Several commenters urged that applicants without past performance records should not be penalized for lack of those records.

Response: No change has been made. The regulations permit applicants to submit documentation of past performance in any activities related to the management and conduct of a research and training activity. The Secretary believes it is valid to assign some value to prior experience as an indicator of future performance, and notes further that this is only one of many selection criteria.

Comment: Some commenters urged that a specified and more significant weight be assigned to the criterion of past performance.

Response: No change has been made. The Secretary believes peer reviewers should consider the factor of past performance in the context of all other factors that indicate the quality of the research and training activity that the applicant is likely to conduct.

Comment: Several commenters suggested that NIDRR change references to the staff of an RRTC in § 352.31(d) to reflect more accurately the different staff positions typically found in RRTC's. They stated that the typical Center has a single project director and several principal investigators, and may have a research director and a training director.

Response: A change has been made. The regulations now refer to a project director, research director, training director, and other key staff.

Comment: One commenter requested that physical restoration or medical rehabilitation be specified in the list of rehabilitation problems in § 350.1(a)(1).

Response: A change has been made. The Secretary agrees that physical restoration is an important area of rehabilitation research and should be emphasized in the regulations.

Comment: Several commenters recommended that site visits be part of the peer review of all highly rated applicants for awards above $299,000 per year.

Response: No change has been made. The regulations (§ 350.35) now permit the Secretary to exercise discretion in deciding to visit as many highly rated applicants as necessary to arrive at a fair decision.

Comment: One commenter suggested that the definition of older American Indians as fifty-five years or older, compared to sixty years or older for all other groups, was discriminatory.

Response: No change has been made. The Rehabilitation Act of 1973, as amended, defines older American Indians as those aged fifty-five years or older, and all other older individuals as those aged sixty years or older.

Comment: One commenter questioned the wisdom of requiring collaborative research in the RRTC's (§ 352.31(a)(2)). The commenter suggested that unusual skill and sophistication are required to conduct that research and that the expertise may not always be available to conduct this activity in an appropriate manner.

Response: No change has been made. The criterion in the regulations refers to "appropriate interdisciplinary and collaborative research activities." This does not require Centers to conduct

collaborative research, and would not even award positive consideration to collaborative research that was other than appropriate. Further, this is only one of the factors that peer reviewers will use in assessing the relevance and importance of the applicant's proposed research program.

Comment: Several commenters suggested that the requirement that Centers develop training packages and materials in forms suitable for individuals with all types of disabilities is unnecessary and impractical. Some commenters suggested that this should be limited to preparing materials in forms accessible to the target group of the particular Center, and others urged that the phrase "when appropriate" be inserted.

Response: A change has been made. The regulations now require that Centers prepare training and related materials in alternate media usable by individuals with a variety of types of disabilities. The Secretary intends that Centers make their materials accessible to a broad range of individuals with disabilities, regardless of whether the disability is a target of the Center's work.

Comment: One commenter suggested NIDRR specify that the site visit to an applicant for a grant should include a non-Federal member of the peer review team.

Response: No change has been made. While it is likely that a non-Federal peer reviewer will be involved in nearly all site visits, the Secretary does not want to preclude the use of a Federal peer reviewer when that individual possesses the most appropriate expertise for the assignment.

Comment: One commenter suggested that, in limiting the indirect charges that RRTC host institutions may collect, NIDRR has made an unnecessary reference to Education Department General Administrative Regulations (EDGAR) provisions concerning limitations on overhead for training.

Response: No change has been made. The indirect cost limitation included in the Rehabilitation Act Amendments of 1986 provides an exception to the EDGAR limitation on indirect costs for training projects as well as to the Common Accounting Procedures of the Office of Management and Budget (OMB). Since Part 75 of EDGAR applies generally to NIDRR research grants, it is necessary to indicate when certain EDGAR provisions are inapplicable.

Comment: One commenter urged that the regulations be amended to permit applicants for REC's to submit videotapes as part of their application packages.

Response: No change has been made. The NIDRR regulations do not address the form in which applicants submit applications, and thus do not preclude the use of videotapes. However, NIDRR cannot guarantee that all peer reviewers will have the facilities to view all types of videotapes. Information affecting the form of applications is contained in the Application Package, a separate document. NIDRR will consider including guide lines for the appropriate use of videotapes in future revisions to its Application Package.

Comment: One commenter suggested that the requirement that the research conducted in an RRTC should be relevant to the needs of individuals with disabilities in the geographic area would exclude individuals from other geographic areas from participating in the research programs.

Response: No change has been made. This provision is included in the Rehabilitation Act of 1973, as amended. The Secretary intends that this provision be met by a Center's providing a sufficient clincial population to conduct research in the specified priority area. NIDRR does not preclude individuals from any area of the country from seeking treatment in any NIDRR-sponsored RRTC.

Comment: One commenter stated that NIDRR should specify that RRTC's must be affiliated with clinical rehabilitation facilities in order to assure relevance to a clinical population.

Response: No change has been made. Linkage with a clinical rehabilitation program is already a requirement for RRTC's.

Comment: One commenter urged that § 351.10 be amended to specifically authorize Research and Demonstration projects to study communication factors affecting rehabilitation.

Response: A change has been made. The Secretary agrees that problems in communication are among the important factors affecting rehabilitations.

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