DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Ch. I

[Docket No. 88N-0004]

Pediatric Dosing Information for Over-the-Counter Human Drugs; Intent and Request for Information

AGENCY: Food and Drug Administration.

ACTION: Notice of intent.

SUMMARY: The Food and Drug Administration (FDA) is considering proposing a rule concerning dosing information in the labeling of over-the-counter (OTC) drug products for children under 12 years of age. The agency is considering this action because of advisory review panel recommendations, agency proposals, and comments that have been submitted to other rulemakings as part of the ongoing review of OTC drug products conducted by FDA. The agency is not proposing any regulatory changes in this notice. The purpose of this notice is to present a number of matters that the agency would like interested persons to address and to give interested persons an opportunity to (1) submit comments on how pediatric dosing information should be presented in the labeling of OTC drug products, and (2) present information and data on related issues and problems.

DATES: Written comments by October 18, 1988, and reply comments by November 17, 1988.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gibertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the course of FDA's OTC drug review, the advisory review panels that evaluated the safety and effectiveness of OTC drug products and the agency have given particular consideration to appropriate labeling and dosage directions for children. This document discusses the panels' recommendations concerning pediatric dosing information, the agency's proposed pediatric dosage labeling, and comments submitted in response to the panels' recommendatons and agency proposals.

The "OTC Volumes" cited in this document are on public display in the Dockets Management Branch.

I. Advisory Review Panel Recommendations Concerning Pediatric Dosages and the Agency's Adoption of These Recommendations

The advisory review panels varied in their recommendations concerning pediatric dosages for OTC drug products intended for systemic absorption as follows: The basis for their recommendations, the age ranges recommended, and the relationship between children's dosage levels and adult dosage levels. In general, the agency has accepted the panels' recommendations concerning pediatric dosing information and adopted labeling based on these recommendations in tentative final and final monographs for OTC drug products. The following are examples of the various recommendations.

A. Internal Analgesic OTC Drug Products

The Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel) reviewed the pediatric dosages in the labeling of internal analgesic/antipyretic drug products that were submitted to it (42 FR 35346; July 8, 1977) and noted the absence of a "recognized" pediatric dosage schedule for internal analgesic drug products (42 FR 35366). Data and information submitted to the Panel indicated that the pediatric dosages described in the labeling submitted to it provided children's dosage levels that are too low to be effective (Refs. 1 and 2). The Panel also reviewed the medical literature and standard references such as "AMA Drug Evaluations" (Ref. 3) and the "United States Pharmacopeia 19th Revision" (Ref. 4) to ascertain a basis for appropriate pediatric dosages for internal analgesic drug products (42 FR 35367). In determining the appropriate basis for pediatric dosages, the Panel discussed both the relationship between a child's body surface area and age and between a child's body weight and age (42 FR 35367 and 35368). Because the relationship between body surface area and age for children from ages 3 to 12 years is linear, and the relationship between body weight and age for children in this age group is nonlinear after the age of 7 years, the Panel based its pediatric dosage recommendations for internal analgesics upon the 1.5 grams/meter^2 body surface area daily dosage for that age as described by Done (Ref. 5).

For aspirin and acetaminophen, the Panel recommended a standard adult dosage unit of 325 milligrams (mg) and a standard pediatric dosage unit of 80 mg. Based on these dosage units, the Panel recommended the following pediatric dosages for aspirin and acetaminophen to be given every 4 hours up to five times a day while symptoms or fever persists, or as directed by a physician:

PANEL'S RECOMMENDED DIRECTIONS FOR PEDIATRIC DOSAGES OF ASPIRIN AND ACETAMINOPHEN

Age (years)	Pediatric (80-mg) dosage units		Adult (325-mg) dosage units	
	Number dosage units	Dosage in mg	Number dosage units	Dosage in mg
Under 2	(1)	(1)	(1)	(1)
2 to under 4	2	160	½	162.5
4 to under 6	3	240	¾	243.8
6 to under 9	4	320	1	325.0
9 to under 11	5	400	1¼	406.3
11 to under 12	6	480	1½	487.5

(1) Consult a doctor.

The agency plans to accept, with minor modifications, the Internal Analgesic Panel's recommended dosages for children for aspirin and acetaminophen in the proposed rule for OTC internal analgesic drug products, to be published in a future issue of the **Federal Register.** The agency plans to propose the following directions for pediatric dosages of acetaminophen, aspirin, and sodium salicylate:

AGENCY'S PROPOSED DIRECTIONS FOR PEDIATRIC DOSAGES OF ACETAMINOPHEN, ASPIRIN, AND SODIUM SALICYLATE

Age (years)	Number of 80-mg or 81-mg (1) dosage units	Number of 325-mg (1) dosage units
Under 2	Consult a doctor	Consult a doctor.
2 to under 4.	2	½.
4 to under 6.	3	¾.
6 to under 9.	4	1.
9 to under 11.	4 to 5	1 to 1¼.
11 to under 12.	4 to 6	1 to 1½.

(1) Dose may be repeated every 4 hours while symptoms persist, up to five times a day or as directed by a doctor.

References

(1) OTC Volume 030142, Docket No. 77N-0094, Dockets Management Branch.

(2) Clayton, J., *in* "Transcripts of Proceedings, Internal Analgesic Panel," pp. 1–8, April 9, 1976, Dockets Management Branch.
(3) "AMA Drug Evaluations," 2d Ed., American Medical Association, Chicago, pp. 264–265, 1973.
(4) "The Pharmacopeia of the United States of America," 19th Revision, The United States Pharmacopeial Convention, Inc., Rockville, MD, 1975.
(5) Done, A.K., *in* "Proceedings of the Conference on Effects of Chronic Salicylate Administration," edited by R.M. Lamont-Havers and B.W. Wagner, U.S. Government Printing Office, Washington, 1966.

B. Antiemetic OTC Drug Products

The Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (Laxative Panel) made recommendations concerning pediatric dosages for these classes of drug products, but did not specifically discuss the basis for its recommendations (40 FR 12902; March 21, 1975). The Panel made the following dosage recommendations for antiemetic drug products:

Cyclizine hydrochloride. The oral dosage for children 6 to 12 years of age is 25 mg up to three times daily. The oral dosage for adults is 50 to 200 mg daily.

Dimenhydrinate. The oral dosage for children 2 to 6 years of age is 12.5 to 25 mg up to three times daily and the oral dosage for children 6 to under 12 years of age is 25 mg up to three times daily. The adult oral dosage is 200 to 400 mg daily in four divided doses.

Meclizine hydrochloride. No oral dosage for children was recommended. The oral dosage for adults is 25 to 50 mg once daily.

In the final rule for OTC antiemetic drug products (52 FR 15886; April 30, 1987), the agency established dosages for the monograph ingredients that, except for dimenhydrinate, are consistent with the dosages recommended by the Laxative Panel. The agency added dosages for diphenhydramine hydrochloride and established the following dosages for OTC antiemetic drug products in the monograph:

(1) *For products containing cyclizine hydrochloride.* Adult oral dosage is 50 mg every 4 to 6 hours, not to exceed 200 mg in 24 hours or as directed by a doctor. For children 6 to under 12 years of age, the oral dosage is 25 mg every 6 to 8 hours, not to exceed 75 mg in 24 hours or as directed by a doctor.

(2) *For products containing dimenhydrinate.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours, not to exceed 400 mg in 24 hours or as directed by a doctor. For children 6 to under 12 years of age, the oral dosage is 25 to 50 mg every 6 to 8 hours, not to exceed 150 mg in 24 hours or as directed by a doctor. For children 2 to under 6 years of age, the oral dosage is 12.5 to 25 mg every 6 to 8 hours, not to exceed 75 mg in 24 hours or as directed by a doctor.

(3) *For products containing diphenhydramine hydrochloride.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours or as directed by a doctor. For children 6 to under 12 years of age, the oral dosage is 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours or as directed by a doctor.

(4) *For products containing meclizine hydrochloride.* No oral dosage for children was recommended. The oral dosage for adults is 25 to 50 mg once daily or as directed by a doctor.

C. Miscellaneous Internal OTC Drug Products

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel) provided pediatric dosage recommendations for anthelmintic drug products (45 FR 59540; September 9, 1980). Although the Panel did not discuss the basis for pediatric dosages for this class of drugs, it stated that OTC pinworm medication is not recommended for infants and children under 2 years of age or weighing less than 25 pounds (lb), except under the supervision of a physician. The Panel recommended weight-based dosages for pinworm active ingredients for both adults and children over 2 years of age.

In the final rule for OTC anthelmintic drug products (51 FR 27756; August 1, 1986), the agency adopted the Miscellaneous Internal Panel's dosage recommendations for the treatment of pinworm infestation with the active ingredient pyrantel pamoate, i.e., for adults (over 12 years) and children 2 to under 12 years of age, the oral dosage is a single dose of 5 mg per lb or 11 mg per kilogram (kg) of body weight not to exceed 1 gram (g). The agency also included in the monograph the following table that specifies dosages in mg for specified body weight ranges:

DIRECTIONS FOR DOSAGES OF ANTHELMINTIC DRUG PRODUCTS BASED ON WEIGHT

Weight	Dosage (taken as a single dose)[1]
Less than 25 pounds or under 2 years old.	Do not use unless directed by a doctor.
25 to 37 pounds	125 milligrams.
38 to 62 pounds	250 milligrams.
63 to 87 pounds	375 milligrams.
88 to 112 pounds.	500 milligrams.
113 to 137 pounds.	625 milligrams.
138 to 162 pounds.	750 milligrams.
163 to 187 pounds.	875 milligrams.
188 pounds and over.	1,000 milligrams.

[1] Depending on the product, the label should state the quantity of drug as a liquid measurement (e.g., teaspoonsful) or as the number of dosage units (e.g., tablets) to be taken for the varying body weights. (If appropriate, it is recommended that a measuring cup graduated by body weight and/or liquid measurement be provided with the product.) Manufacturers should present this information as appropriate for their product and may vary the format of this chart as necessary.

D. Cough-Cold OTC Drug Products

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Cough-Cold Panel) recommended children's dosage directions for many OTC cough-cold active ingredients (41 FR 38312; September 9, 1976). That Panel, stating that it was aware that data on the use in children of most cough-cold drug products was negligible or nonexistent, acknowledged that cough-cold drug products are widely used in the pediatric patient population (41 FR 38333). The Panel stated that optimum dosages of a drug in adults and children are dependent on factors such as the drug itself; individual patient variables such as special sensitivity or tolerance to the specific drug; the age and weight of the patient; and metabolic, pathologic, or psychological conditions in the patient. The Panel believed that, ideally, pediatric dosages should be derived from clinical trials with children, but recognized the extreme difficulties attendant upon such trials. The Panel stated that, traditionally, pediatric dosage calculations for infants and children have been based on body surface area, weight, or age of the child as a proportion of the "usual adult dose." The Panel recognized that determining children's dosages based on age, although convenient, may be the least reliable method because of the large variation in weight of patients at a specific age. However, the Panel stated that OTC drug products have a wide margin of safety and recommended that children's dosages be based on age. The Panel sought the assistance of a panel of experts in pediatric drug therapy (41 FR 38333) in establishing appropriate children's dosages for OTC cough-cold

drug products. Based on the recommendation of that panel of experts, the Panel recommended that for infants under 2 years of age, the pediatric dosage should be established by a physician; for children 2 to under 6 years of age, the dosage be one-fourth the adult dosage; and for children 6 to under 12 years of age, the dosage be one-half the adult dosage. Accordingly, the recommended dosages for children for the active ingredients included in the Panels recommended monograph were based on these dosage guidelines.

Although the Cough-Cold Panel recommended OTC pediatric dosages for children 2 to under 6 years of age for antitussive, 'bronchodilator, expectorant, and nasal decongestant drug products, it recommended that dosages for children in this age group for antihistamine drug products be placed in the professional labeling section of the monograph, i.e., for use only under the advice and supervision of a physician.

In general, the agency adopted the Cough-Cold Panel's recommended dosages for children in proposed rules for OTC antihistamine drug products (50 FR 2200; January 15, 1985 and 52 FR 31892; August 24, 1987), OTC nasal decongestant drug products (50 FR 2220; January 15, 1985), and OTC antitussive drug products (48 FR 48576; October 19, 1983), and in the final rule for OTC antitussive drug products (52 FR 30042; August 12, 1987).

In the proposed rule for OTC antihistamine drug products (50 FR 2200 and 52 FR 31892), the agency established that the OTC dosages for all Category I active ingredients for children 6 to under 12 years of age is one-half the adult dose. In addition, the agency concurred with the Panel and proposed in the tentative final monograph that pediatric dosages for children 2 to under 6 years be placed in the professional labeling section of the monograph (50 FR 2217 and 52 FR 31914). For one drug, chlorcyclizine, the professional labeling included the dosages for both children 6 to under 12 years of age and 2 to under 6 years of age. The professional labeling dosages for all Category I active ingredients, with the exception of triprolidine hydrochloride, for children 2 to under 6 years of age is one-fourth the adult dose. The proposed professional labeling dosages for triprolidine hydrochloride are an oral dose of 0.938 mg every 4 to 6 hours, not to exceed 3.744 mg in 24 hours, for children 4 to under 6 years of age (approximately 37.5 percent of the adult dose); an oral dose of 0.625 mg every 4 to 6 hours, not to exceed 2.5 mg in 24 hours, for children 2 to under 4 years of age (25 percent of the adult dose); and an oral dose of 0.313 mg every 4 to 6 hours, not to exceed 1.252 mg in 24 hours, for infants 4 months to under 2 years of age (12.5 percent of the adult dose) (52 FR 31914).

In the proposed rule for OTC nasal decongestant drug products (50 FR 2220), the agency's proposed OTC dosages for all Category I oral active ingredients for children 6 to under 12 years of age are one-half the adult dose and for children 2 to under 6 years of age are one-fourth the adult dose.

In the final rule for OTC antitussive drug products (52 FR 30042), the agency's established OTC dosages for all monograph oral active ingredients for children 6 to under 12 years of age are one-half the adult dose. The OTC dosages for all Category I active ingredients, except chlophedianol hydrochloride and codeine preparations, for children 2 to under 6 years of age is one-fourth the adult dose. The dosage for chlophedianol hydrochloride for children 2 to under 6 years of age is one-half rather than one-fourth the adult dose and is restricted to use under the supervision of a physician (i.e., is included in the professional labeling section of the monograph). Dosages for codeine preparations for children 2 to under 6 years of age are also restricted to use under the supervision of a physician and are included under the professional labeling section of the monograph. The following dosages for codeine preparations for children 2 to under 6 years of age are weight-based and a calibrated measuring device is required for use in children in this age group:

For products containing codeine ingredients identified in § 341.14(a)(2). (1) Children 2 to under 6 years of age: Oral dosage is 1 mg per kg 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 kg), the oral dosage is 3 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours; for children 3 years of age (average body weight, 14 kg), the oral dosage is 3.5 mg every 4 to 6 hours, not to exceed 14 mg in 24 hours; for children 4 years of age (average body weight, 16 kg), the oral dosage is 4 mg every 4 to 6 hours, not to exceed 16 mg in 24 hours; for children 5 years of age (average body weight, 18 kg), the oral dosage is 4.5 mg every 4 to 6 hours, not to exceed 18 mg in 24 hours. 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. 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.

II. Comments on Pediatric Dosing Information

In response to the pediatric dosage recommendations of the Cough-Cold Panel and the agency's proposals concerning the Panel's recommendations for antihistamine, antitussive, and nasal decongestant drug products, the agency has received comments from four manufacturers and one manufacturers' association requesting that the pediatric dosages for cough-cold drug products be revised to provide a greater subdivision of age ranges for children under 12 years of age that would more closely approximate weight-based dosages. The comments' revised dosages are based on a standardized pediatric dosing unit and standardized dosing age ranges (as described below) for the drugs in these categories. Copies of these comments are on public display in the Dockets Management Branch (Ref. 1). The agency notes that similar requests for this pediatric dosage revision have not been received in other OTC drug rulemakings to date.

In response to the tentative final monograph for OTC antihistamine drug products (50 FR 2200 and 52 FR 31892), the agency has received comments from one manufacturer and one manufacturers' association requesting that the pediatric dosages for children 2 to under 6 years of age for antihistamine drug products be included in the OTC labeling directions in the monograph. Copies of these comments are on public display in the Dockets Management Branch (Ref. 2).

References

(1) Comment Nos. C00197, C00200, C00201, 00204, C00206, C00207, C00208, C00209, 00210, C00211, CR0005, CR0006, in OTC Volume 00PDNI, Docket No. 88N–0004, Dockets Management Branch.

(2) Comment Nos. C00210 and C00211 in OTC Volume 00PDNI, Docket No. 88N–0004, Dockets Management Branch.

A. Standardized Pediatric Dosage Units

In general, the comments stated that it is important to achieve a consistent approach to pediatric dosing of OTC drug products in the marketplace and in the agency's rulemakings and 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. The comments pointed out that there are significant differences between the pediatric dosing schedules recommended by the Internal Analgesic Panel for internal analgesic drug products (42 FR 35346) and the agency's pediatric dosing schedules for cough-cold drug products such as antihistamines and nasal decongestants. The comments explained that the agency's children's dosages for OTC antihistamine, antitussive, and nasal decongestant drug products provide only two age ranges for children under 12 years of age (6 to under 12 years and 2 to under 6 years, with professional labeling only for the use of antihistamines in the under 6 age group) whereas the Panel's recommendations for the children's dosages for internal analgesics provided the following five age ranges with shorter age spans for children under 12 years of age: 11 to under 12 years, 9 to under 11 years, 6 to under 9 years, 4 to under 6 years, and 2 to under 4 years. According to the comments, the pediatric dosage schedule for internal analgesics is better than the dosage schedules for cough-cold drug products because the internal analgesic dosage schedule correlates more closely with the practice of basing children's dosages to body weight. The comments stated that the use of body weight is widely accepted by pediatricians as a preferred method of determining drug dosages for children. In addition, it is well recognized that variations in weight have a significant impact on appropriate dosage levels for different individuals, and that body weight varies significantly with age for children between the ages of 2 and 12 years because this is a period of rapid growth. Therefore, it is appropriate to have a greater subdivision of age ranges in the recommended dosages for the 2- to 12-year age group so that the dosages correspond better to body weight variations due to rapid growth.

The comments recommended that a standard pediatric dosing unit be established based on both weight and age considerations and suggested that a good standard pediatric dosing unit would be one-eighth of the adult dose. This standard pediatric dosing unit would correlate with 6-lb increments as a child grows and could be used with the 50th percentile weights for age ranges to produce the following dosing increments for the given age and weight ranges (Ref. 1):

COMMENTS' SUGGESTED STANDARDIZED PEDIATRIC DOSING SCHEDULE

Age (years)	Weight (lb)	Appropriate number of dosing units [1]
4 months to under 1	12 to 17	1
1 to under 2	18 to 23	1.5
2 to under 4	24 to 35	2
4 to under 6	36 to 47	3
6 to under 9	48 to 59	4
9 to under 11	60 to 71	5
11 to under 12	72 to 95	6
12 and over	96 and over	8

[1] 1 dosing unit equals one-eighth adult dose.

The comments pointed out that applying the above dosing schedule to OTC drug products would not result in doses that exceed the currently proposed doses for internal analgesics where toxicity is a real concern, and yet would prevent underdosing of older children at the top end of the cough-cold dosing age range of 6 to under 12 years.

One comment requested that the directions for use for OTC oral antitussive drug products proposed in the tentative final monograph be modified to improve the OTC dosage schedules for children 2 to 12 years of age. The comment specifically addressed the agency's proposed dosage schedule in § 341.74(d)(1)(iv) for dextromethorphan and dextromethorphan hydrobromide (48 FR 48594) 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. The comment submitted a report and literature references in support of a safe and effective dose range of 0.3 to 0.5 mg/kg for dextromethorphan and in support of weight-based, age-related dosage schedules for children under 12 years of age in general (Ref. 2).

The comment contended that its recommended dosage schedule provides improvements over the agency's proposed dosage schedule in that it provides more age subdivisions for children under 12 years of age to assure more consistent dosage in a particular dosage range, and it provides a weight-based dosage schedule for children 2 to under 12 years of age that supplements the age-based dosage schedule.

In 1986, the American Academy of Pediatrics considered the dosing recommendations in the tentative final monographs for OTC antihistamine, antitussive, and nasal decongestant drug products and encouraged the agency to accept the comments' recommendations to adopt the more weight-based, age-related dosage ranges for children's dosages of OTC drug products (Ref. 3).

References

(1) Minutes of Meeting, dated February 25, 1985, "Changing Children's Dosage Schedules for OTC Antihistamine and Nasal Decongestant Drug Products to Provide More Age Intervals, to Add Weight-Based Dosages, and to Extend OTC Package Labeling Dosage Schedules for Antihistamines Down to 2 Years of Age," identified as MM00002, Docket No. 76N–052H, Dockets Management Branch.

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

(3) Letters from R.J. Roberts, Chairman, Committee on Drugs, American Academy of Pediatrics, to W.E. Gilbertson, FDA, OTC Volume 00PDNI, Docket No. 88N–0004, Dockets Management Branch.

1. *Weight ranges in OTC pediatric labeling.* The comments also recommended that OTC drug labeling should consider the needs of children who are in the 10th or 90th percentile ranges for weight by including weight ranges in addition to age ranges for dosing. One comment requested that manufacturers be permitted to include pediatric dosages based on weight in the labeling of OTC drug products because it is a medically sound alternative. Several comments stated that an additional benefit of optionally available weight-related dosages is that they can be used when a child's weight is known, especially for children that are very large or very small for their age or when children approach the usual age breaks for a given dosing schedule. The comments explained further that dosing

for drugs in the pediatric patient has been recommended on the basis of age, weight, and body surface area; however, there are specific advantages to each of these approaches to determine the proper dose for a pediatric patient. While body surface area may be the most accurate parameter to use in determining the proper dose for a child, body surface area is not a parameter that is commonly used by pediatricians and it is clearly not a parameter that is used by parents. Because changes in weight are reasonably similar to changes in body surface area and the weight of a child is more likely to be known to a pediatrician or a parent than body surface area, dosing based on weight is a reasonable substitute for dosing based on body surface area. However, a child's weight is not always known at the time that a physician recommends a dosage or at the time that a parent is determining the proper dose for a child. Because the age of a child is almost always know, it is the simplest parameter for consumer use in determining the appropriate dose for a child. The comments stated that age can be used as a reasonable guide to growth in the child provided that the wide variations in growth that occur in children are taken into consideration. The comments concluded that weight-based dosages offer a significant benefit for those consumers or health professionals who would like to dose by weight, but that weight-based dosages should be optional in labeling because weight is not always known. The comments also stated that, in order to avoid unnecessary consumer and health professional confusion when such weight-based dosages are made available, all pediatric product labeling that provides weight-based dosages should use the standardized weight schedule provided in the table above.

2. *Standardized pediatric dosages as optional labeling.* Several comments recommended that the pediatric dosage labeling based on more finely subdivided age ranges be optional. One comment requested that this dosage labeling be optional and that it be added to the current dosages in the tentative final monographs to accommodate products intended primarily for pediatric populations. Other comments stated that for those products targeted toward adults, which also provide dosage recommendations for the pediatric patient, it is reasonable to continue to allow the option of using dosages proposed in the tentative final monographs, i.e., dosages for the age ranges 2 to under 6 years and 6 to under 12 years. Other comments did not request that the pediatric dosage labeling based on more finely subdivided age ranges be optional.

3. *Professional labeling for children under 2 years.* Two comments from the same manufacturer recommended that dosages based on the standardized pediatric dosage unit for children under 2 years of age be added to the professional labeling sections of the nasal decongestant and antihistamine monographs. The comments recommended that dosages for nasal decongestant and antihistamine drug products should be as follows: for children 1 year of age, one and one-half times the standardized pediatric dosage unit (one pediatric dosage unit equals one-eighth the adult dose) and for children 4 to 11 months, one standardized pediatric dosage unit. One of the comments provided specific dosages for children 4 and under 24 months of age based on the above standardized pediatric dosage units for the active ingredients acetaminophen, chlorpheniramine, destromethorphan, and pseudoephedrine (Ref. 1). Another comment from the same manufacturer recommended that the following dosages for dextromethorphan based on weight and age for children under 2 years of age be added to the professional labeling sector of the antitussive monograph:

COMMENT'S SUGGESTED PEDIATRIC DOSING SCHEDULE FOR DEXTROMETHORPHAN

Weight		Age (months)	Dextromethorphan	
(kg)	(lb)		Dose every 4–6 hours (mg)	Dosing range (mg/kg)
2.5–5.4	6–11	Under 4	1.25	0.23–0.50
5.5–7.9	12–17	4–11	2.5	0.32–0.45
8.0–10.9	18–23	12–23	3.75	0.34–0.47

Reference

(1) Comment No. C00211, Docket No. 76N–052H, Dockets Management Branch.

4. *Pediatric dosage labeling for OTC cough-cold combination drug products.* Several comments noted that OTC antihistamines, antitussives, nasal decongestants, and internal analgesics are often combined. In order to allow for combination drug products to be labeled with consistent pediatric dosage information, these comments requested that the agency adopt children's dosages for antihistamines, antitussives, and nasal decongestants that are similar to and consistent with the pediatric dosages for internal analgesics. One comment stated that, for products primarily intended for pediatric use, revised cough-cold pediatric dosages similar to those for analgesic/antipyre dosages would provide consistency among various monographs and allow for consistency in the formulation of combination drug products.

Another comment from a manufacturer stated that the dosages for children 6 to under 12 years of age proposed in the antihistamine tentative final monograph (§ 341.72(d); 50 FR 2216 to 2217) cannot be reconciled with the dosage recommendations of the Internal Analgesic Panel (Pediatric Schedule C; 42 FR 35368). The comment stated further that the combination of a Category I antihistamine and a Category I analgesic/antipyretic has been recommended by both the Cough-Cold Panel (41 FR 38326) and the Internal Analgesic Panel (42 FR 35370). Thus, the comment contended, the 6- to under 12-year age group should not be deprived of the benefit of such a combination drug product. The comment recommended specific pediatric dosages for chlorpheniramine that are consistent with the dosages for analgesic/antipyretic ingredients and that would allow pediatric combination drug products containing these ingredients. The comment contended that no significant safety issue would be involved in allowing such combinations.

Another comment from the same manufacturer stated that there is a need to harmonize the dosage regimens of cough-cold ingredients and internal analgesic/antipyretic ingredients for pediatric use and that failure to provide for consistency in these pediatric dosages for cough-cold and analgesic/antipyretic drug products would result in the removal from the market of combination drug products intended for use in children under 12 years of age. However, the comment did not provide any examples of specific products that would be removed from the market. The comment stated that the agency should not ignore the reality that nasal congestion frequently occurs concurrently with fever and/or pain in children as well as adults. Further, for concurrent symptoms, the administration of few rather than many dosage units to children will meet with less resistance, thereby increasing patient compliance and benefit. The comment provided several examples of the problems that would arise in providing appropriate pediatric dosages for combination drug products containing oral nasal decongestants and analgesics/antipyretics because of the inconsistencies in the dosage

recommendations for these classes of drugs (Ref. 1). The comment stated that these examples emphasize the need for intermonograph consistency for pediatric dosages and that the alternative to consistency among monograph dosages would be a plethora of dosage forms or label directions which would only confuse the consumer needlessly.

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 (48 FR 48594) is incompatible with the pediatric dosage schedule proposed by the Internal Analgesic Panel for aspirin or acetaminophen. The comment argued that the Internal Analgesic Panel's recommended limitation of the maximum daily pediatric doses of aspirin of acetaminophen to no more than five 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 five 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 five rather than six doses. 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 the dextromethorphan.

Reference

(1) Comment No. C00200, Docket No. 76N-052N, Dockets Management Branch.

B. OTC Labeling of Antihistamine Drug Products for Children 2 to Under 6 Years of Age

One comment presented data from a survey of 200 pediatricians concerning these physicians' use of OTC cough-cold and internal analgesic drug products in children as well as their preferences for the pediatric labeling of these drug products (Ref. 1). When asked whether the pediatricians recommend the use of these products in children in the age ranges of 2 to 5 years and 6 to 14 years, over 90 percent said that they did recommend use in both age ranges with the exception of aspirin. Responses to how the pediatricians determine the dose of cough-cold or internal analgesic drugs for children varied widely from using the "Physician's Desk Reference" (PDR) or pediatric handbooks to personal experience in using the drugs in children. The comment pointed out that these wide variations in determining pediatric doses lead to inconsistent dosing of children. Although the proposed OTC drug labeling provides a basis for consistency in dosing for children 6 years of age and over, dosing for children under 6 years is less consistent if the OTC drug labeling, e.g., the proposed antihistamine labeling, does not provide dosages for children in this age group. The pediatricians were asked for their preferences in dosing parameters in the labeling of OTC drug products, i.e., age, weight, age *and* weight, body surface, or other parameter. The majority (61 to 63 percent) said that they would prefer age *and* weight dosing parameters in the OTC labeling of antihistamines, antitussives, nasal decongestants, and internal analgesics. The survey revealed that the majority (51 percent) of the pediatricians believe that pediatric dosing information for children under 2 years of age in OTC drug labeling would be "very beneficial" and an additional 34 percent believe such labeling would be "somewhat beneficial." In response to a question concerning the comfort level of including pediatric dosing information in OTC drug labeling, most pediatricians expressed a "high comfort level" with such labeling.

Reference

(1) Comment No. C00211, Docket No. 76N-052H, Dockets Management Branch.

III. Agency Response Regarding Changes in Pediatric Dosing Information for OTC Drug Products

After reviewing these comments and other pertinent information, the agency has determined that additional information is required before it will be able to ascertain whether changes are needed in the manner in which pediatric dosing information is presented in the labeling of OTC drug products. The agency is publishing this notice of intent and request for information to elicit further comments and/or data concerning pediatric dosages. The agency is inviting further public comment on the following matters concerning pediatric dosages: (1) Should the agency retain only its current general schedule for pediatric dosing information (i.e., ages 2 to under 6 and 6 to under 12) or expand this format, (2) if the answer is to expand, then how many additional age ranges should be included, and what should these age subdivisions be, (3) should a standard pediatric dosing schedule based on both weight and age be adopted, (4) if the answer is yes, how should this schedule be designated, (5) should this expanded pediatric dosage labeling be required for all OTC drug products or should it be optional, (6) what OTC drug products should this schedule apply to—both to class and dosage form, (7) if an expanded dosage schedule is adopted, are calibrated dosing devices necessary to ensure that the more finely subdivided dosages are accurately administered, and (8) is it safe to provide pediatric dosages for children 2 to under 6 years of age in the OTC labeling directions for antihistamine drug products?

In addressing these questions, consideration should be given to the following factors:

1. A number of comments presented good reasons why additional pediatric age subdivisions and/or weight-based, age-related dosages are scientifically and medically sound and would be beneficial in OTC drug labeling. However, some of these comments requested that such pediatric dosage labeling be optional and stated that it would be reasonable to allow products that are targeted primarily for adults, but that also provide pediatric dosage information in the labeling, to continue to use the pediatric dosage directions proposed in the tentative final monographs. The comments did not elaborate further as to why the requested changes in the pediatric dosage information should not be applicable to all products that contain

pediatric dosage labeling. The reasons for requesting that inconsistent pediatric dosage information be allowed for different types of cough-cold products is unclear. The agency questions why, if the greater subdivision of age ranges in the 2- to 12-year age group provides better dosing that corresponds to body weight variations, this dosing information should not appear on the labeling of all applicable OTC drug products.

2. The agency has received comments recommending revised pediatric dosages for only antihistamine, antitussive, and nasal decongestant drug products. These revised dosages are similar to the pediatric dosing concept that was proposed by the Internal Analgesic Panel for internal analgesic/antipyretic drug products. If the more detailed pediatric dosages are appropriate for the above categories of drugs, it would seem they should also apply to other types of OTC drug products, e.g., expectorants, systemic bronchodilators, antiemetics, and/or systemic laxatives. The basis for requesting more finely subdivided pediatric dosage age ranges for some cough-cold products is that dosages that correlate more closely with weight will provide better dosing of children during the rapid growth age range between 2 and 12 years of age. This reasoning would seem to apply to any systemic drug product. In order to provide consistency in the agency's approach to pediatric dosage directions, the agency would like to identify which drug classes should be affected by revised pediatric dosages and any information that would support a different approach for different drug classes that include systemic drug products. The agency also invites comment as to whether greater age/weight variations would be pertinent for topically applied OTC drugs.

3. The comments did not mention the use of calibrated dosing devices for liquid dosage forms in general to ensure that the requested dosages, which are more finely subdivided than the currently proposed doses, will be given to the child accurately. The agency requests comments as to whether it would be appropriate to direct parents to use calibrated measuring devices for liquid products to facilitate and ensure that the more finely divided doses are administered as accurately as possible when they are given to the child. The agency also invites comments concerning the manner in which solid dosage forms should be formulated to ensure accurate dosing of children, e.g., providing tablets that contain no more than one-eighth to one-fourth the adult dose.

4. For many years, the use of antihistamine drug products in children 2 to under 6 years of age has been restricted to use only under the supervision of a physician. The Cough-Cold Panel did not recommend that dosage labeling for this age group be included in the OTC labeling for antihistamine drug products. The Panel recommended that such labeling be placed in the professional labeling section of the monograph (41 FR 38312), and the agency agreed with the Panel's recommendations in the tentative final monograph (50 FR 2200 and 52 FR 31914). No data concerning the safety of OTC use of antihistamines in children 2 to under 6 years of age were submitted by comments that requested that dosages for this age group be included in the OTC labeling of these drug products. The agency believes that evaluation of information concerning the safety of antihistamine use in children 2 to under 6 years of age without the supervision of a physician is necessary before the agency can make a decision concerning the switch of dosage labeling for this age group for antihistamines from professional use only to OTC labeling for consumer use. The agency is particularly concerned with the safety of OTC use of the antihistamines diphenhydramine hydrochloride and doxylamine succinate in children 2 to under 6 years because these antihistamines produce more drowsiness and depress the central nervous system to a greater extent than other OTC antihistamine ingredients. The agency believes that the use of calibrated measuring devices for these antihistamine drug products in liquid dosage forms and the formulation of solid dosage forms to restrict the amount of ingredient per dosage unit may be necessary to ensure accurate administration of the dosages to children and to prevent possible toxicity in children 2 to under 6 years due to an overdose of an antihistamine drug product. The agency requests specific comment on this matter.

Decisions to revise pediatric dosage labeling in the absence of studies in children that support the safety and effectiveness of such dosage labeling are particularly difficult. The agency requests the submission of further data and information pertinent to the matters discussed above as well as the safety and effectiveness of the requested revised dosage levels for children under 12 years of age. The agency is not proposing any regulatory changes in this document. After the agency evaluates all of the comments, data, and information received, it will determine whether it should propose any regulatory changes in the manner in which pediatric dosing information is presented in the labeling of OTC drug products. Based on the comments, data, and information received, if the agency determines that information concerning the use of antihistamine drug products should appear in the OTC labeling, appropriate proposals to amend the monograph for OTC antihistamine drug products will be made in a future issue of the **Federal Register**.

Interested persons may, on or before October 18, 1988, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this notice of intent and request for information. Three copies of all comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before November 17, 1988.

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

Dated: April 22, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

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