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References

The references are provided for informational purposes and are optional reading.

1. Monograph
2. Clinical
3. Clinical/Pharmacology
4. Consumer Healthcare Products Association (CHPA)
5. E11 Guidance Document
6. PREA Guidance
7. Allergic Rhinitis: Clinical Development Programs for Drug Products

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Antitussive	10/19/83 (48 FR 48576)	8/12/87 (52 FR 30042)
Bronchodilator	10/26/82 (47 FR 47520)	10/2/86 (51 FR 35326)
Expectorant	7/9/82 (47 FR 30002)	2/28/889 (54 FR 8494)
Nasal Decongestant	1/15/85 (50 FR 2220)	8/23/94 (59 FR 43386)

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.

[FR Doc. 88-13830 Filed 6-17-88; 8:45 am]

BILLING CODE 4160-01-M

III. List of Active Ingredients

Cold, Cough. Allergy, Bronchodilator and Antiasthmatic Drug Products
for Over-the-Counter Human use

Pharmacologic Group	Active Ingredients
Antihistamine	Brompheniramine maleate Chlorpheniramine maleate Dexchlorpheniramine maleate Diphenhydramine hydrochloride Phenindamine tartrate Pyrilamine maleate Triprolidine hydrochloride Chlorcyclizine hydrochloride Dexbrompheniramine maleate Diphenhydramine citrate Doxylamine succinate Pheniramine maleate Thonzylamine hydrochloride
Antitussive	Codeine -- Codeine phosphate -- Codeine sulfate Dextromethorphan Diphenhydramine citrate **Topical** - Camphor - Menthol Dextromethorphan hydrobromide Diphenhydramine hydrochloride
Bronchodilator	Ephedrine Ephedrine sulfate Epinephrine bitartrate Racepinephrine hydrochloride Ephedrine hydrochloride Epinephrine Racephedrine hydrochloride
Expectorant	Guaifenesin
Nasal Decongestant	Phenylephedrine hydrochloride Pseudoephedrine sulfate Pseudoephedrine hydrochloride Phenylephedrine bitartrate in an effervescent dosage form **Topical** Levmetamfetamine Ephedrine hydrochloride Naphazoline hydrochloride Phenylephrine HCl Oxymetazoline HCl Ephedrine Ephedrine sulfate Oxymetazoline hydrochloride Propylhexedrine

Single Ingredient Drug Facts Label

Drug Facts

Active Ingredients (in each 5ml teaspoonful) ***Purpose***

Dextromethorphan HBr 7.5 .....cough suppressant

Uses

- temporarily relieves cough associated with common cold

Warnings

Do not use in a child who is taking prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson' disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product.

Ask a doctor before use if the child has

- a sodium-restricted diet
- a cough accompanied by excessive phlegm (mucus)
- a persistent or chronic cough such as occurs with asthma

When using this product

- **do not exceed recommended dosage**

Stop use and ask a doctor if

- cough persists for more than 1 week, tends to recur or is accompanied by fever, rash, or persistent headache. This could be signs of a serious condition.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- if needed, repeat dose every 6-8 hours
- do not exceed 4 doses in 24 hours

children 6 to under 12 years	2 teaspoonfuls
children 2 to under 6 years	1 teaspoonful
children under 2 years	Consult a doctor

Other information

- **each teaspoonful contains:** sodium 19 mg
- store at 20 – 25°C (68 - 77°F)
- avoid excessive heat (40°C, 104°F)
- read all warnings and directions before use. Keep carton.

Inactive ingredients [list ingredients in alphabetical order]

Questions or comments? Call **1-800-XXX-XXXX:** [insert appropriate times when the phone will be answered by a person, e.g., weekdays 8AM to 11 PM EST; weekends 9AM to 11 PM, EST]

Triple Ingredients Drug Facts Label

Drug Facts

Active Ingredients (in each 0.8 mL) ***Purpose***

Acetaminophen 80 mg .....Pain reliever/fever reducer

Dextromethorphan HBr 2.5 mg .....cough suppressant

Phenylephrine HCl 1.25 mg .....Nasal decongestant

Uses Temporarily relieves these cold symptoms:

- minor aches and pains • headache • nasal congestion • cough • stuffy nose

Warnings

- **Liver warning:** This product contains acetaminophen. Severe liver damage may occur if the child takes
  - more than 5 doses in 24 hours
  - with other drugs containing acetaminophen
- **Sore throat warning:** If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, nausea or vomiting, consult a doctor.

Do not use

- with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure
- in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, emotional conditions or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product.
- with any other product containing acetaminophen

Ask a doctor before use if the child has

- liver disease • heart disease • high blood pressure • thyroid disease • diabetes
- persistent or chronic cough such occurs with asthma
- cough that occurs with too much phlegm (mucus)

Stop use and ask a doctor if

- nervousness, dizziness or sleeplessness occurs
- pain, nasal congestion or cough gets worse or lasts for more then 5 days
- fever gets worse or lasts for more than 3 days
- redness or swelling is present
- new symptoms occurs
- cough comes back or occurs with fever, rash or headache that lasts. These could be signs of a serious condition

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use this product during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **this product does not contain directions or warnings for adults use**
- **do not give more than directed**
- shake well before using
- find right dose on chart below. If possible, use weight
- use only enclosed dosing syringe specifically designed for use with this product
- do not use any other dosing device
- fill to dose level
- dispense liquid slowly into child's mouth, toward inner cheek
- if needed, repeat dose every 4 hours
- do not give more than 5 times in 24 hours
- replace bottle cap to maintain child resistance

Weight	Age	Dose
Under 24 lbs	Under 2 years	Call a doctor
24 – 35 lbs	2 – 3 years	1.6 ml = 0.8 ml + 0.8 ml

Other information

- store at 20 – 25°C (68 - 77°F)
- avoid excessive heat (40°C, 104°F)
- read all warnings and directions before use. Keep carton.

Inactive ingredients [list ingredients in alphabetical order]

Questions or comments? Call **1-800-XXX-XXXX: [**

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Guidance for Industry

E11 Clinical Investigation of Medicinal Products in the Pediatric Population

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

ICH
December 2000

Guidance for Industry

E11 Clinical Investigation of Medicinal Products in the Pediatric Population

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U.S. Department of Health and Human Services
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ICH

December 2000

Table of Contents

Guidance for Industry[1]

E11 Clinical Investigation of Medicinal Products in the Pediatric Population

I. INTRODUCTION (1.)

A. Objectives of the Guidance (1.1)

The number of medicinal products currently labeled for pediatric use is limited. This guidance is intended to encourage and facilitate timely pediatric medicinal product development internationally. The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population.

B. Background (1.2)

Other ICH documents with relevant information affecting pediatric studies include:

- E2: Clinical Safety Data Management
- E3: Structure and Content of Clinical Study Reports
- E4: Dose-Response Information to Support Drug Registration
- E5: Ethnic Factors in the Acceptability of Foreign Clinical Data
- E6: Good Clinical Practice: Consolidated Guideline
- E8: General Considerations for Clinical Trials
- E9: Statistical Principles for Clinical Trials

[1] This guidance was prepared under the auspices of the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

E10: Choice of Control Group in Clinical Trials
M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
Q1: Stability Testing
Q2: Validation of Analytical Procedures
Q3: Impurity Testing

C. Scope of the Guidance (1.3.)

Specific clinical study issues addressed in this guidance include:

1. Considerations when initiating a pediatric program for a medicinal product;
2. Timing of initiation of pediatric studies during medicinal product development;
3. Types of studies (pharmacokinetic, pharmacokinetic/pharmacodynamic (PK/PD), efficacy, safety);
4. Age categories; and
5. Ethics of pediatric clinical investigation.

This guidance is not intended to be comprehensive; other ICH guidances, as well as documents from regional regulatory authorities and pediatric societies, provide additional detail.

D. General Principles (1.4)

Pediatric patients should be given medicines that have been appropriately evaluated for their use in those populations. Safe and effective pharmacotherapy in pediatric patients requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages and, often, the development of pediatric formulations of those products. Advances in formulation chemistry and in pediatric study design will help facilitate the development of medicinal products for pediatric use.

Drug development programs should usually include the pediatric patient population when a product is being developed for a disease or condition in adults and it is anticipated the product will be used in the pediatric population. Obtaining knowledge of the effects of medicinal products in pediatric patients is an important goal. However, this should be done without compromising the well-being of pediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole.

II. GUIDANCE (2)

A. Issues When Initiating a Pediatric Medicinal Product Development Program (2.1)

Data on the appropriate use of medicinal products in the pediatric population should be generated unless the use of a specific medicinal product in pediatric patients is clearly inappropriate. The timing of initiation of clinical studies in relation to studies conducted in adults, which may be influenced by regional public health and medical needs, is discussed in section II.C. Justification for the timing and the approach to the clinical program needs to be clearly addressed with regulatory authorities at an early stage and then periodically during the medicinal product development process. The pediatric development program should not delay completion of adult studies and availability of a medicinal product for adults.

The decision to proceed with a pediatric development program for a medicinal product, and the nature of that program, involve consideration of many factors, including:

- The prevalence of the condition to be treated in the pediatric population
- The seriousness of the condition to be treated
- The availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy and the adverse event profile (including any unique pediatric safety issues) of those treatments
- Whether the medicinal product is novel or one of a class of compounds with known properties
- Whether there are unique pediatric indications for the medicinal product
- The need for the development of pediatric-specific endpoints
- The age ranges of pediatric patients likely to be treated with the medicinal product
- Unique pediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues
- Potential need for pediatric formulation development

Of these factors, the most important is the presence of a serious or life-threatening disease for which the medicinal product represents a potentially important advance in therapy. This situation suggests relatively urgent and early initiation of pediatric studies.

Information from nonclinical safety studies to support a pediatric clinical program is discussed in ICH M3. It should be noted that the most relevant safety data for pediatric studies ordinarily come from adult human exposure. Repeated dose toxicity studies, reproduction toxicity studies, and genotoxicity tests would generally be available. The need for juvenile animal studies should be considered on a case-by-case basis and be based on developmental toxicology concerns.

B. Pediatric Formulations (2.2)

There is a need for pediatric formulations that permit accurate dosing and enhance patient compliance. For oral administration, different types of formulations, flavors, and colors may be more acceptable in one region than another. Several formulations, such as liquids, suspensions, and chewable tablets, may be needed or desirable for pediatric patients of different ages. Different drug concentrations in these various formulations may also be

needed. Consideration should also be given to the development of alternative delivery systems.

For injectable formulations, appropriate drug concentrations should be developed to allow accurate and safe administration of the dose. For medicinal products supplied as single-use vials, consideration should be given to dose-appropriate single-dose packaging.

The toxicity of some excipients may vary across pediatric age groups and between pediatric and adult populations (e.g., benzyl alcohol is toxic in the preterm newborn). Depending on the active substance and excipients, appropriate use of the medicinal product in the newborn may require a new formulation or appropriate information about dilution of an existing formulation. International harmonization on the acceptability of formulation excipients and of validation procedures would help ensure that appropriate formulations are available for the pediatric population everywhere.

C. Timing of Studies (2.3)

During clinical development, the timing of pediatric studies will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatments. Since development of pediatric formulations can be difficult and time consuming, it is important to consider the development of these formulations early in medicinal product development.

1. Medicinal Products for Diseases Predominantly or Exclusively Affecting Pediatric Patients (2.3.1)

In such cases, the entire development program will be conducted in the pediatric population except for initial safety and tolerability data, which will usually be obtained in adults. Some products may reasonably be studied only in the pediatric population even in the initial phases (e.g., when studies in adults would yield little useful information or expose them to inappropriate risk). Examples include surfactant for respiratory distress syndrome in preterm infants and therapies targeted at metabolic or genetic diseases unique to the pediatric population.

2. Medicinal Products Intended to Treat Serious or Life-Threatening Diseases, Occurring in Both Adults and Pediatric Patients, for Which There Are Currently No or Limited Therapeutic Options (2.3.2)

The presence of a serious or life-threatening disease for which the product represents a potentially important advance in therapy suggests the need for relatively urgent and early initiation of pediatric studies. In such cases, medicinal product development should begin early in the pediatric population, following assessment of initial safety data and reasonable evidence of potential benefit. Pediatric study results should be part of the marketing

application database. In circumstances where this has not been possible, lack of data should be justified in detail.

3. *Medicinal Products Intended to Treat Other Diseases and Conditions (2.3.3)*

In such cases, although the medicinal product will be used in pediatric patients, there is less urgency than in previous cases, and studies would usually begin at later phases of clinical development or, if a safety concern exists, even after substantial postmarketing experience in adults. Companies should have a clear plan for pediatric studies and reasons for their timing. Testing of these medicinal products in the pediatric population would usually not begin until phase 2 or 3. In most cases, therefore, only limited pediatric data would be available at the time of submission of the application, but more would be expected after marketing. The development of many new chemical entities is discontinued during or following phase 1 and 2 studies in adults for lack of efficacy or an unacceptable side effect profile. Therefore, very early initiation of testing in pediatric patients might needlessly expose these patients to a compound that will be of no benefit.

In cases of a nonserious disease where the medicinal product represents a major therapeutic advance for the pediatric population, studies should begin early in development, and pediatric data should be submitted in the application. Lack of data should be justified in detail. Thus, it is important to carefully weigh benefit/risk and therapeutic need in deciding when to start pediatric studies.

D. Types of Studies (2.4)

The principles outlined in ICH E4, E5, E6, and E10 apply to pediatric studies. Several pediatric-specific issues are worth noting. When a medicinal product is studied in pediatric patients in one region, the intrinsic (e.g., pharmacogenetic) and extrinsic (e.g., diet) factors[2] that could affect the extrapolation of data to other regions should be considered.

When a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and pediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of pediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in

[2] In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different drug responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively.

adults. If this approach is taken, adult pharmacokinetic data should be available to plan the pediatric studies.

When a medicinal product is to be used in younger pediatric patients for the same indication(s) as those studied in older pediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger pediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of pediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for pediatric use.

An approach based on pharmacokinetics is likely to be insufficient for medicinal products where blood levels are known or expected not to correspond with efficacy or where there is concern that the concentration-response relationship may differ between the adult and pediatric populations. In such cases, studies of the clinical or the pharmacological effect of the medicinal product would usually be expected.

Where the comparability of the disease course or outcome of therapy in pediatric patients is expected to be similar to adults, but the appropriate blood levels are not clear, it may be possible to use measurements of a pharmacodynamic effect related to clinical effectiveness to confirm the expectations of effectiveness and to define the dose and concentration needed to attain that pharmacodynamic effect. Such studies could provide increased confidence that achieving a given exposure to the medicinal product in pediatric patients would result in the desired therapeutic outcomes. Thus, a PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies.

In other situations where a pharmacokinetic approach is not applicable, such as for topically active products, extrapolation of efficacy from one patient population to another can be based on studies that include pharmacodynamic endpoints and/or appropriate alternative assessments. Local tolerability studies may be appropriate. It may be important to determine blood levels and systemic effects to assess safety.

When novel indications are being sought for the medicinal product in pediatric patients or when the disease course and outcome of therapy are likely to be different in adults and pediatric patients, clinical efficacy studies in the pediatric population are recommended.

1. Pharmacokinetics (2.4.1)

Pharmacokinetic studies generally should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations. Relative bioavailability comparisons of pediatric formulations with the adult oral formulation typically should be done in adults. Definitive pharmacokinetic studies for dose selection across the age ranges of pediatric patients in

whom the medicinal product is likely to be used should be conducted in the pediatric population.

Pharmacokinetic studies in the pediatric population should generally be conducted in patients with the disease. This may lead to higher intersubject variability than studies in normal volunteers, but the data will better reflect clinical use.

For medicinal products that exhibit linear pharmacokinetics in adults, single-dose pharmacokinetic studies in the pediatric population may provide sufficient information for dosage selection. This can be corroborated, if indicated, by sparse sampling in multidose clinical studies. Any nonlinearity in absorption, distribution, and elimination in adults and any difference in duration of effect between single and repeated dosing in adults would suggest the need for steady state studies in the pediatric population. All these approaches can be facilitated by knowledge of adult pharmacokinetic parameters. Knowing the pathways of clearance (renal and metabolic) of the medicinal product and understanding the age-related changes of those processes can often be helpful in planning pediatric studies.

Dosing recommendations for most medicinal products used in the pediatric population are usually based on milligram (mg)/kilogram (kg) body weight up to a maximum adult dose. While dosing based on mg/square meter body surface area might be preferred, clinical experience indicates that errors in measuring height or length (particularly in smaller children and infants) and calculation errors of body surface area from weight and height are common. For some medications (e.g., medications with a narrow therapeutic index, such as those used in oncology), surface-area-guided dosing may be necessary, but extra care should be taken to ensure proper dose calculation.

Practical considerations to facilitate pharmacokinetic studies

The volume of blood withdrawn should be minimized in pediatric studies. Blood volumes should be justified in protocols. Institutional review boards/independent ethics committees (IRBs/IECs) review and may define the maximum amount of blood (usually on a milliliters (mL)/kg or percentage of total blood volume basis) that may be taken for investigational purposes. Several approaches can be used to minimize the amount of blood drawn and/or the number of venipunctures.

- Sensitive assays for parent drugs and metabolites to decrease the volume of blood required per sample

- Laboratories experienced in handling small volumes of blood for pharmacokinetic analyses and for laboratory safety studies (blood counts, clinical chemistry)

- Collection of routine, clinical blood samples wherever possible at the same time as samples are obtained for pharmacokinetic analysis

- The use of indwelling catheters, to minimize distress as discussed in section II.E.5.

- Use of population pharmacokinetics and sparse sampling based on optimal sampling theory to minimize the number of samples obtained from each patient. Techniques include (1) sparse sampling approaches where each patient contributes as few as 2 to 4 observations at predetermined times to an overall *population area-under-the-curve* and (2) population pharmacokinetic analysis using the most useful sampling time points derived from modeling of adult data.

2. *Efficacy (2.4.2)*

The principles in study design, statistical considerations, and choice of control groups detailed in ICH E6, E9, and E10 generally apply to pediatric efficacy studies. There are, however, certain features unique to pediatric studies. The potential for extrapolation of efficacy from studies in adults to pediatric patients or from older to younger pediatric patients is discussed in section II.D. Where efficacy studies are going to be conducted, companies may want to develop, validate, and employ different endpoints for specific age and developmental subgroups. Measurement of subjective symptoms, such as pain, calls for different assessment instruments for patients of different ages. In pediatric patients with chronic diseases, the response to a medicinal product may vary among patients not only because of the duration of the disease and its chronic effects but also because of the developmental stage of the patient. Many diseases in the preterm and term newborn infant are unique or have unique manifestations precluding extrapolation of efficacy from older pediatric patients and call for novel methods of outcome assessment.

3. *Safety (2.4.3)*

ICH guidances on E2 topics and ICH E6, which describe adverse event reporting, apply to pediatric studies. Age-appropriate, normal laboratory values and clinical measurements should be used in adverse event reporting. Unintended exposures to medicinal products (accidental ingestions) may provide the opportunity to obtain safety and pharmacokinetic information and to maximize understanding of dose-related side effects.

Medicinal products may affect physical and cognitive growth and development, and the adverse event profile may differ in pediatric patients. Because developing systems may respond differently from matured adult organs, some adverse events and drug interactions that occur in pediatric patients may not be identified in adult studies. In addition, the dynamic processes of growth and development may not manifest an adverse event acutely, but at a later stage of growth and maturation. Long-term studies or surveillance data, either while patients are on chronic therapy or during the posttherapy period, may be needed to determine possible effects on skeletal, behavioral, cognitive, sexual, and immune maturation and development.

4. *Postmarketing Information (2.4.4)*

Normally the pediatric database is limited at the time of approval. Therefore, postmarketing surveillance is particularly important. In some cases, long-term follow-up studies may be important to determine effects of certain medications on growth and development of pediatric patients. Postmarketing surveillance and/or long-term follow-up studies may provide safety and/or efficacy information for subgroups within the pediatric population or additional information for the entire pediatric population.

E. Age Classification of Pediatric Patients (2.5)

Any classification of the pediatric population into age categories is to some extent arbitrary, but a classification such as the one below provides a basis for thinking about study design in pediatric patients. Decisions on how to stratify studies and data by age should take into consideration developmental biology and pharmacology. Thus, a flexible approach is necessary to ensure that studies reflect current knowledge of pediatric pharmacology. The identification of which ages to study should be medicinal product-specific and justified.

If the clearance pathways of a medicinal product are well established and the ontogeny of the pathways is understood, age categories for pharmacokinetic evaluation might be chosen based on any *break point* where clearance is likely to change significantly. Sometimes, it may be more appropriate to collect data over broad age ranges and examine the effect of age as a continuous covariant. For efficacy, different endpoints may be established for pediatric patients of different ages, and the age groups might not correspond to the categories presented below. Dividing the pediatric population into many age groups might needlessly increase the number of patients required. In longer term studies, pediatric patients may move from one age category to another; the study design and statistical plans should prospectively take into account changing numbers of patients within a given age category.

The following is one possible categorization. There is, however, considerable overlap in developmental (e.g., physical, cognitive, and psychosocial) issues across the age categories. Ages are defined in completed days, months, or years.

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years (dependent on region))

1. Preterm Newborn Infants (2.5.1)

The study of medicinal products in preterm newborn infants presents special challenges because of the unique pathophysiology and responses to therapy in this population. The complexity of and ethical considerations involved in studying preterm newborn infants suggest the need for careful protocol development with expert input from neonatologists

and neonatal pharmacologists. Only rarely will it be possible to extrapolate efficacy from studies in adults or even in older pediatric patients to the preterm newborn infant.

The category of preterm newborn infants is not a homogeneous group of patients. A 25-week gestation, 500-gram (g) newborn is very different from a 30-week gestation newborn weighing 1,500 g. A distinction should also be made for low-birth-weight babies as to whether they are immature or growth retarded. Important features that should be considered for these patients include:

1. gestational age at birth and age after birth (adjusted age);
2. immaturity of renal and hepatic clearance mechanisms;
3. protein binding and displacement issues (particularly bilirubin);
4. penetration of medicinal products into the central nervous system (CNS);
5. unique neonatal disease states (e.g., respiratory distress syndrome of the newborn, patent ductus arteriosus, primary pulmonary hypertension);
6. unique susceptibilities of the preterm newborn (e.g., necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity);
7. rapid and variable maturation of all physiologic and pharmacologic processes leading to different dosing regimens with chronic exposure; and
8. transdermal absorption of medicinal products and other chemicals.

Study design issues that should be considered include:

1. weight and age (gestational and postnatal) stratification;
2. small blood volumes (a 500-g infant has 40 mL of blood);
3. small numbers of patients at a given center and differences in care among centers; and
4. difficulties in assessing outcomes.

2. Term Newborn Infants (0 to 27 days) (2.5.2)

Although term newborn infants are developmentally more mature than preterm newborn infants, many of the physiologic and pharmacologic principles discussed above also apply to term infants. Volumes of distribution of medicinal products may be different from those in older pediatric patients because of different body water and fat content and high body-surface-area-to-weight ratio. The blood-brain barrier is still not fully mature and medicinal products and endogenous substances (e.g., bilirubin) may gain access to the CNS with resultant toxicity. Oral absorption of medicinal products may be less predictable than in older pediatric patients. Hepatic and renal clearance mechanisms are immature and rapidly changing; doses may need to be adjusted over the first weeks of life. Many examples of increased susceptibility to toxic effects of medicinal products result from limited clearance in these patients (e.g., chloramphenicol grey baby syndrome). On the other hand, term newborn infants may be less susceptible to some types of adverse effects (e.g., aminoglycoside nephrotoxicity) than are patients in older age groups.

3. *Infants and Toddlers (28 days to 23 months) (2.5.3)*

This is a period of rapid CNS maturation, immune system development, and total body growth. Oral absorption becomes more reliable. Hepatic and renal clearance pathways continue to mature rapidly. By 1 to 2 years of age, clearance of many drugs on a mg/kg basis may exceed adult values. The developmental pattern of maturation is dependent on specific pathways of clearance. There is often considerable inter-individual variability in maturation.

4. *Children (2 to 11 years) (2.5.4)*

Most pathways of drug clearance (hepatic and renal) are mature, with clearance often exceeding adult values. Changes in clearance of a drug may be dependent on maturation of specific metabolic pathways.

Specific strategies should be addressed in protocols to ascertain any effects of the medicinal product on growth and development. Children achieve several important milestones of psychomotor development that could be adversely affected by CNS-active drugs. Entry into school and increased cognitive and motor skills may affect a child's ability to participate in some types of efficacy studies. Factors useful in measuring the effects of a medicinal product on children include skeletal growth, weight gain, school attendance, and school performance. Recruitment of patients should ensure adequate representation across the age range in this category, as it is important to ensure a sufficient number of younger patients for evaluation. Stratification by age within this category is often unnecessary, but it may be appropriate to stratify patients based on pharmacokinetic and/or efficacy endpoint considerations.

The onset of puberty is highly variable and occurs earlier in girls, in whom normal onset of puberty may occur as early as 9 years of age. Puberty can affect the apparent activity of enzymes that metabolize drugs, and dose requirements for some medicinal products on a mg/kg basis may decrease dramatically (e.g., theophylline). In some cases, it may be appropriate to specifically assess the effect of puberty on a medicinal product by studying pre- and postpubertal pediatric patients. In other cases, it may be appropriate to record Tanner stages of pubertal development or obtain biological markers of puberty and examine data for any potential influence of pubertal changes.

5. *Adolescents (12 to 16-18 years (dependent on region)) (2.5.5)*

This is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development. In certain studies, pregnancy testing and review of sexual activity and contraceptive use may be appropriate.

This is also a period of rapid growth and continued neurocognitive development. Medicinal products and illnesses that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt and, by changing the pattern of growth, may

affect final height. Evolving cognitive and emotional changes could potentially influence the outcome of clinical studies.

Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.

Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol, and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.

F. Ethical Issues in Pediatric Studies (2.6)

The pediatric population represents a vulnerable subgroup. Therefore, special measures are needed to protect the rights of pediatric study participants and to shield them from undue risk. The purpose of this section is to provide a framework to ensure that pediatric studies are conducted ethically.

To be of benefit to those participating in a clinical study, as well as to the rest of the pediatric population, a clinical study must be properly designed to ensure the quality and interpretability of the data obtained. In addition, participants in clinical studies should benefit from the clinical study except under the special circumstances discussed in ICH E6.

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC) (2.6.1)

The roles and responsibilities of IRBs and IECs, as detailed in ICH E6, are critical to the protection of study participants. When protocols involving the pediatric population are reviewed, there should be IRB/IEC members or experts consulted by the IRB/IEC who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.

2. Recruitment (2.6.2)

Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)or legal guardian or the study participant.

Reimbursement and subsistence costs may be covered in the context of a pediatric clinical study. Any compensation should be reviewed by the IRB/IEC.

When studies are conducted in the pediatric population, an attempt should be made to include individuals representing the demographics of the region and the disease being studied, unless there is a valid reason for restricting enrollment.

3. Consent and Assent (2.6.3)

As a rule, a pediatric subject is legally unable to provide informed consent. Therefore pediatric study participants are dependent on their parent(s) or legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand. Where appropriate, participants should assent to enroll in a study (age of assent may be determined by IRBs and IECs or be consistent with local legal requirements). Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form, or the written informed consent. In all cases, participants should be made aware of their rights to decline to participate or to withdraw from the study at any time. Attention should be paid to signs of undue distress in patients who are unable to clearly articulate their distress. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s) or legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In such a situation, continued parental or legal guardian consent should be sufficient to allow participation in the study. Emancipated or mature minors (defined by local laws) may be capable of giving autonomous consent.

Information that can be obtained in a less vulnerable, consenting population should not be obtained in a more vulnerable population or one in which the patients are unable to provide individual consent. Studies in handicapped or institutionalized pediatric populations should be limited to diseases or conditions found principally or exclusively in these populations, or situations in which the disease or condition in these pediatric patients would be expected to alter the disposition or pharmacodynamic effects of a medicinal product.

4. Minimizing Risk (2.6.4)

However important a study may be to prove or disprove the value of a treatment, participants may suffer injury as a result of inclusion in a study, even if the whole community benefits. Every effort should be made to anticipate and reduce known hazards. Investigators should be fully aware before the start of a clinical study of all relevant preclinical and clinical toxicity of the medicinal product. To minimize risk in pediatric clinical studies, those conducting the study should be properly trained and experienced in

studying the pediatric population, including the evaluation and management of potential pediatric adverse events.

In designing studies, every attempt should be made to minimize the number of participants and of procedures, consistent with good study design. Mechanisms should be in place to ensure that a study can be rapidly terminated should an unexpected hazard be identified.

5. Minimizing Distress (2.6.5)

Repeated invasive procedures may be painful or frightening. Discomfort can be minimized if studies are designed and conducted by investigators experienced in the treatment of pediatric patients.

Protocols and investigations should be designed specifically for the pediatric population (not simply re-worked from adult protocols) and approved by an IRB or IEC as described in section II.F.1.

Practical considerations to ensure that participants' experiences in clinical studies are positive and to minimize discomfort and distress include the following:

- Personnel knowledgeable and skilled in dealing with the pediatric population and its age-appropriate needs, including skill in performing pediatric procedures
- A physical setting with furniture, play equipment, activities, and food appropriate for age
- The conduct of studies in a familiar environment such as the hospital or clinic where participants normally receive their care
- Approaches to minimize discomfort of procedures, such as (1) topical anesthesia to place IV catheters, (2) indwelling catheters rather than repeated venipunctures for blood sampling, and (3) collection of some protocol-specified blood samples when routine clinical samples are obtained.

IRBs and IECs should consider how many venipunctures are acceptable in an attempt to obtain blood samples for a protocol and ensure a clear understanding of procedures if an indwelling catheter fails to function over time. The participant's right to refuse further investigational procedures should always be respected except as noted in section II.F.3.

Guidance for Industry

How to Comply with the Pediatric Research Equity Act

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Grace Carmouze, 301-594-7337 or Leonard Wilson, 301-827-0373.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 2005
Procedural

Guidance for Industry

How to Comply with the Pediatric Research Equity Act

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Contains Nonbinding Recommendations

Draft – Not for Implementation

GUIDANCE FOR INDUSTRY[1]

How to Comply with the Pediatric Research Equity Act

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance provides recommendations on how to interpret the pediatric study requirements of the Pediatric Research Equity Act (Public Law 108-155) (PREA). PREA amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 505B (21 U.S.C. 355B). PREA requires the conduct of pediatric studies for certain drug and biological products.[2] Specifically, PREA requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (see section 505B(a) of the Act). It also authorizes FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of the changes enumerated above (hereinafter "marketed drugs and biological products") to submit a pediatric assessment under certain circumstances (see section 505B(b) of the Act).

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[1] This guidance has been prepared by the PREA Working Group at the Food and Drug Administration (FDA).

[2] For purposes of this guidance, references to "drugs" and "drug and biological products" includes drugs approved under section 505 of the Act (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.

Paperwork Reduction Act Public Burden Statement: According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The draft guidance contains information collections approved in OMB Nos. 0910-0001 (expires May 31, 2008) and 1910-0433 (expires March 31, 2007). In addition, the time required to complete this information collection is estimated to average from 8 to 50 hours per response, including the time to prepare and submit an application containing required studies or request a waiver from such studies.

Although PREA applies to both new applications (or supplements to applications) and already marketed drugs and biological products, this guidance will only provide recommendations on NDAs and BLAs (or supplements to an already approved application) for drugs and biological products under section 505B(a) of the Act. Issues under section 505B(b) of the Act related to already marketed drug and biological products for which the sponsor is not seeking one of the enumerated changes may be addressed in future guidance.

This guidance addresses the pediatric assessment,[3] the pediatric plan (see section V.A), waivers and deferrals, compliance issues, and pediatric exclusivity provisions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On December 3, 2003, the Pediatric Research Equity Act (PREA) was signed into law. PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling. In PREA, Congress codified many of the elements of the Pediatric Rule, a final rule issued by FDA on December 2, 1998 (63 FR 66632), and suspended by court order on October 17, 2002.[4]

Under the Pediatric Rule, approval actions taken or applications submitted on or after April 1, 1999, for changes in active ingredient, indication, dosage form, dosing regimen, or route of administration were required to include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred. The Pediatric Rule was designed to work in conjunction with the *pediatric exclusivity* provisions of section 505A of the Act (21 U.S.C. 355a), an incentive signed into law to encourage sponsors or holders of approved applications to voluntarily perform the pediatric studies described in a Written Request[5] issued by FDA, in order to qualify for an additional 6 months of marketing exclusivity.

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[3] For purposes of this guidance, the term "pediatric assessment" describes the required submissions under PREA that contain data, primarily from required pediatric clinical studies, that are adequate to assess safety and effectiveness and support dosing and administration for claimed indications in all relevant pediatric populations (section 505B(a)(1) and (2) of the Act). Generally, the terms "pediatric assessment" and "pediatric studies" are used interchangeably.

[4] The Pediatric Rule was codified at 21 CFR 314.55 and 601.27, with additional amendments to 21 CFR 201, 312, 314, and 601.

[5] FDA issues Written Requests for pediatric studies under 21 U.S.C. 355a.

On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109) was enacted. The BPCA reauthorized and amended the pediatric exclusivity incentive program of section 505A and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to conduct voluntarily. On April 24, 2002, FDA issued an advance notice of proposed rulemaking (ANPRM) soliciting comments on the most appropriate ways to update the Pediatric Rule in a manner consistent with other mechanisms for obtaining studies created by the BPCA.

On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule and the court suspended its implementation and enjoined its enforcement (Association of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D. D.C. 2002)). When the Court enjoined FDA from enforcing the Pediatric Rule in October 2002, the ANPRM was also rendered obsolete.

As noted above, PREA codified elements of the suspended Pediatric Rule and attempted to fill gaps left by the Pediatric Rule's suspension.

III. OVERVIEW — REQUIREMENTS OF PREA

A. PREA Statutory Requirements

PREA requires all applications (or supplements to an application) submitted under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act). It also authorizes FDA to require holders of approved NDAs and BLAs for marketed drugs and biological products to conduct pediatric studies under certain circumstances (section 505B(b) of the Act).

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations. Products intended for pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant pediatric population.

B. Scope of Requirements

1. Applications Affected by PREA

Because section 4(b) of PREA makes the legislation retroactive, all approved applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration submitted on or after April 1, 1999 (including those approved when the Pediatric Rule was suspended), are subject to PREA. Under PREA, holders of such approved applications that did not previously include pediatric assessments, waivers, or deferrals must submit their pediatric assessments or requests for waiver or deferral (section 4(b)(2)(B) of

PREA). If a waiver request is denied and/or studies are deferred, FDA will require the applicable studies as postmarketing studies. (For additional information on applicable deferral dates, see section IV.B and Attachment C.)

2. Orphan Drugs

PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526."[6] FDA has not issued regulations applying PREA to orphan-designated indications. Thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

3. Generic Drugs Under 505(j) of the Act (21 U.S.C. 355(j))

Because PREA applies only to applications (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and because an abbreviated new drug application (ANDA) submitted under section 505(j) of the Act for a duplicate version of a previously approved drug product does not involve such changes, PREA does not impose pediatric assessment requirements on ANDAs for generic drugs. However, ANDAs submitted under an approved suitability petition under section 505(j)(2)(C) of the Act for changes in dosage form, route of administration, or new active ingredient in combination products are subject to the pediatric assessment requirements that PREA imposes. If clinical studies are required under PREA for a product submitted under an approved suitability petition and a waiver is not granted, that application is no longer eligible for approval under an ANDA.

Because PREA is retroactive, all approved and pending ANDAs submitted on or after April 1, 1999 (when the Pediatric Rule became effective) and prior to December 3, 2003 (when PREA was enacted) under suitability petitions for changes in dosage form, route of administration, or active ingredient in combination products are subject to PREA. Although some ANDAs submitted under suitability petitions after April 1, 1999, and prior to December 3, 2003, would not have been approved as ANDAs had PREA been in effect at the time of approval, PREA's retroactivity does not require FDA to revoke those previous approvals. Instead, as with NDAs and BLAs, holders of approved and pending ANDAs submitted under suitability petitions between April 1, 1999 and December 3, 2003, who have not already obtained waivers, must submit postapproval pediatric studies or a request for a waiver or deferral of the pediatric assessment requirement (section 505B(a)(2) of the Act). If a waiver request is denied for a product already submitted or approved in an ANDA based upon a suitability petition during this time frame, FDA will require the applicable studies as postmarketing studies.

[6] Section 526 is codified at 21 U.S.C. 360bb.

IV. THE PEDIATRIC ASSESSMENT

A. What Is the Pediatric Assessment? (Section 505B(a)(2) of the Act)

Under PREA, the pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to:

- Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations

- Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective

B. When to Submit the Pediatric Assessment in Compliance with PREA

Under PREA, a pediatric assessment must be submitted at the time an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is submitted to the Agency, unless the requirement for the assessment has been deferred or waived. If a deferral has been granted, the pediatric assessment will be due on or before the date specified by the Agency (section 505B(a)(3) of the Act).

As noted above, PREA is retroactive and requires pediatric assessments for all applications submitted between April 1, 1999, and the present. To address potential gaps in pediatric information for applications approved between April 1, 1999, and the present resulting from, among other things, the suspension of the Pediatric Rule in October 2002, PREA provides for waivers or deferrals in cases where pediatric study requirements were never addressed and for extensions of certain deferrals issued previously under the Pediatric Rule (see Attachment C for a chart of deferral dates under PREA).

If an application previously was granted a waiver of pediatric studies under the Pediatric Rule, the waiver will continue to apply under PREA (section 4(b)(2)(A) of PREA).

C. What Types of Data Are Submitted as Part of the Pediatric Assessment?

The data submitted under PREA will depend on the nature of the application, what is known about the product in pediatric populations, and the underlying disease or condition being treated. PREA does not require applicants to conduct separate safety and effectiveness studies in pediatric patients in every case. PREA states:

> If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in

adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

(Section 505B(a)(2)(B)(i) of the Act.)

If extrapolation from adult effectiveness data is inappropriate, adequate and well-controlled efficacy studies in the pediatric population may nevertheless be required. Additional information, such as dosing and safety data, could also be important to support pediatric labeling decisions.

PREA further provides, "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group" (section 505B(a)(2)(B)(ii) of the Act). Whether or not pediatric studies in more than one age group are necessary depends on expected therapeutic benefit and use in each age group, and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. As with the use of adult data, the extrapolation may be supplemented with data to define dosing and safety for the relevant age groups.

Applicants should contact the appropriate review division to discuss the types of pediatric studies needed to complete their pediatric assessments.

V. THE PEDIATRIC PLAN AND SUBMISSIONS

A. When to Develop a Pediatric Plan

A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, the applicant plans to request a waiver or deferral under PREA. Applicants are encouraged to submit their pediatric plans to the Agency as early as possible in the drug development process and to discuss these plans with the Agency at critical points in the development process for a particular drug or biologic.

Early consultation and discussions are particularly important for products intended for life-threatening or severely debilitating illnesses. For these products, FDA encourages applicants to discuss the pediatric plan at pre-investigational new drug (pre-IND) meetings and end-of-phase 1 meetings. For products for life-threatening diseases, the review division will provide its best judgment at the end-of-phase I meetings on whether pediatric studies will be required under PREA and, if so, whether the submission will be deferred until after approval. In general, studies of drugs or biological products for diseases that are life-threatening or severely debilitating in pediatric patients and that lack adequate therapy could begin earlier than studies of other products because the urgency of the need for the products may justify early trials despite the relative lack of safety and effectiveness information.

For products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase 2 meeting. Information to support any planned request for a waiver or deferral of pediatric studies also should be submitted as part of the background package for this meeting. The review division will provide its best judgment about (1) the pediatric assessment that will be required for the product, (2) whether its submission can be deferred, and (3) if deferred, the date studies will be due. In addition, if relevant, FDA encourages applicants to include a discussion of their intent to qualify for and the studies needed to earn pediatric exclusivity (see section VIII for a discussion of PREA and pediatric exclusivity).

When a decision to waive or defer pediatric studies is made at key meetings, the minutes from those meetings reflecting the decision generally will be provided to applicants for their records. Alternatively, a separate letter may be sent to the applicant conveying FDA's decision to either waive or defer the pediatric assessment. If a deferral of studies is granted at the time of the meeting, a due date for submission generally will also be included in the meeting minutes or separate letter.

B. What Ages to Cover in a Pediatric Plan

PREA requires, unless waived or deferred, the submission of a pediatric assessment for certain applications for the claimed indications in all relevant pediatric populations. As discussed in section VI, PREA authorized FDA to waive assessments when: 1) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and 2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act). Thus, PREA requires the pediatric assessment to evaluate safety and effectiveness for the claimed indication(s) for each age group in which the drug or biological product is expected to provide a meaningful therapeutic benefit over existing therapies for pediatric patients or is likely to be used in a substantial number[7] of pediatric patients.

Under PREA, a drug or biological product is considered to represent a *meaningful therapeutic benefit* over existing therapies if FDA estimates that (1) "if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population," or (2) "the drug or biological product is in a class of products or for an indication for which there is a need for additional options" (section 505B(c) of the Act). Improvement over marketed products might be demonstrated by showing (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) enhancement of compliance; or

[7] PREA does not define a "substantial number." In the past, FDA generally has considered 50,000 patients to be a substantial number of patients (see, for example, October 27, 1997, DHHS Public Meeting on FDA's Proposed Regulations to Increase Pediatric Use Information for Drugs and Biologics). The Agency, however, will take into consideration the nature and severity of the condition in determining whether a drug or biological product will be used in a substantial number of pediatric patients.

(4) safety and effectiveness in a new subpopulation for which marketed products are not currently labeled.

The BPCA defines "pediatric studies" or "studies" to include studies in all "pediatric age groups (including neonates in appropriate cases)" in which a drug is anticipated to be used (section 505A(a) of the Act. For purposes of satisfying the requirements of PREA, the appropriate age ranges to be studied may vary, depending on the pharmacology of the drug or biological product, the manifestations of the disease in various age groups, and the ability to measure the response to therapy. In general, however, the pediatric population includes patients age "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" (21 CFR 201.57(f)(9)).

The complex medical state of neonates and infants makes it critical to evaluate drugs specifically for their use. The Agency is also aware that trials in neonates and infants pose special ethical issues. FDA generally will require studies in neonates and infants under PREA if the drug represents an important advancement and use in these age groups for the approved indication is anticipated. However, it is possible that partial waivers for these specific age groups might be appropriate under certain circumstances when "necessary studies are impossible or highly impracticable," or when "there is evidence strongly suggesting that the drug or biologic product would be ineffective or unsafe in that age group" (section 505B(a)(4)(B)(i) and (ii) of the Act).

C. Must the Sponsor Develop a Pediatric Formulation?

PREA requires pediatric assessments to be gathered "using appropriate formulations for each age group for which the assessment is required" (section 505B(a)(2)(A) of the Act). Under PREA, applicants must submit requests for approval of the pediatric formulation used in their pediatric studies, and failure to submit such a request may render the product misbranded (section 505B(d) of the Act). FDA interprets the language "request for approval of a pediatric formulation" to mean that applicants must submit an application or supplemental application for any not previously approved formulation(s) used to conduct their pediatric studies. Where appropriate, applicants may need to begin the development of a pediatric formulation before initiation of pediatric clinical trials.

PREA does, however, specifically authorize FDA to waive the requirement for pediatric studies in one or more age groups requiring a pediatric formulation if the applicant certifies and FDA finds that "the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed" (section 505B(a)(4)(B)(iv) of the Act). This exception is limited to the pediatric groups requiring that formulation (section 505B(a)(4)(C). FDA believes that this partial waiver provision will generally apply to situations where the applicant can demonstrate that unusually difficult technological problems prevented the development of a pediatric formulation. In certain cases, the Agency may seek appropriate external expert opinion (e.g., from an advisory committee) to assess whether a waiver should be granted (see section VI.A and B for more detailed information on waivers).

D. When to Initiate Pediatric Studies

As discussed in section V.A, applicants may initiate pediatric studies of drugs and biologics for life-threatening diseases for which adequate treatment is not available earlier in development than might occur for less serious diseases. The medical need for these products may justify early pediatric trials despite a relative lack of safety and effectiveness data. In some cases, pediatric studies of a drug or biological product for a life-threatening disease may begin as early as phase 1 or phase 2, when the initial safety data in adults become available.

The Agency recognizes that in certain cases scientific and ethical considerations will dictate that pediatric studies should not begin until after approval of the drug or biological product for use by adults — for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit is likely to be low, or the risks of exposing pediatric patients to the new product may not be justified until after the product's safety profile is well established in adults after initial marketing.

The Agency recommends that for products with a narrow therapeutic index, the nature of the disease in the pediatric population to be studied and the context in which the drug will be used should factor into the decision on when to initiate the studies in the affected pediatric patient population. For example, studies for an oncology drug product with a narrow therapeutic index might be conducted in children with a life-threatening cancer at an earlier stage in the drug development process than studies for a new aminoglycoside antimicrobial used to treat acute pyelonephritis infections in children. In the latter case, there are several therapeutic options available, so the investigational drug would likely be studied in children after the approval in adults for this condition.

E. What Information Must Be Submitted to FDA

Pediatric studies of drugs conducted under an investigational new drug application (IND) are subject to the rules governing INDs, including the content and format requirements of 21 CFR 312.23 and the IND safety and annual reporting requirements described in 21 CFR 312.32 and 312.33, respectively.

- When study reports are submitted as part of an application or supplement to an application, the content and format must meet the relevant general requirements for submission (see 21 CFR 314.50 for NDA requirements and 21 CFR 601.2 for BLA requirements).

VI. WAIVERS AND DEFERRALS

A. What Is a Waiver?

PREA authorizes FDA to waive the requirement to submit the pediatric assessment, based on established criteria, for some or all pediatric age groups. FDA can grant a full or partial waiver of the requirements on its own initiative or at the request of an applicant. If an applicant requests

a waiver, the applicant should provide written justification for the waiver and evidence to support the request.

B. How to Apply for a Waiver

1. Criteria for Full Waiver (Section 505B(a)(4)(A) of the Act)

On FDA's initiative or at the request of an applicant, FDA will grant a full waiver of the requirement to submit pediatric assessments if the applicant certifies and FDA finds one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act).

Another example is a drug or biological product for an indication that has extremely limited applicability to pediatric patients because the pathophysiology of these diseases occur for the most part in the adult population. FDA would be likely to grant a waiver for studies on products developed for the treatment of these conditions without requiring applicants to provide additional evidence of impossibility or impracticality. For a list of adult-related conditions that may be candidates for a disease-specific waiver, see Attachment A, Sample Waiver Request Form.

(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups (section 505B(a)(4)(A)(ii) of the Act).

If a waiver is granted based upon evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act).

2. Criteria for Partial Waiver (Section 505B(a)(4)(B) of the Act)

On its own initiative or at the request of an applicant, FDA will grant a partial waiver of the requirement to submit pediatric assessments for a drug or biological product with respect to a specific pediatric age group, if the applicant certifies and FDA finds evidence of one or more of the following:

(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) (section 505B(a)(4)(B)(i) of the Act).

(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(4)(B)(ii) of the Act). If a partial waiver is granted based on evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).

(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group (section 505B(a)(4)(B)(iii) of the Act).

(d) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed (section 505B(a)(4)(B)(iv) of the Act). If a waiver is granted on the basis that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation (section 505B(a)(4)(C) of the Act).

3. Information in a Waiver Request

As noted in section V, discussions with FDA on developing pediatric plans and initiating pediatric studies should occur early in the drug development process. If an applicant believes a full or partial waiver of the pediatric studies requirement is warranted, FDA strongly encourages the applicant to request the waiver at the earliest appropriate time. This guidance includes a sample Waiver Request to assist applicants in providing sufficient information for FDA to determine whether to grant a waiver request (Attachment A). However, the information necessary to support any particular waiver will be determined on a case-by-case basis.

To request a waiver, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in waiver request
- Statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority (i.e., one of 2(a)-(d) in Attachment A)
- Evidence that the request meets the statutory reason(s) for waiver of pediatric assessment requirements
- Applicant Certification

4. Waiver Decision

The Agency will grant a waiver request if FDA determines that any of the criteria for a waiver enumerated in the statute have been met. As noted above, if a full or partial waiver is granted "because there is evidence that a drug or biological product would be ineffective or unsafe in

pediatric populations, this information shall be included in the labeling for the drug or biological product" (section 505B(a)(4)(D) of the Act).

As discussed in section V, for waivers agreed to at the end-of-phase 2 meetings, the meeting minutes will document the waiver of pediatric assessment requirements. Full or partial waiver documentation (meeting minutes or a letter from FDA) should be submitted in the Clinical Data Section of the NDA or BLA and noted in Form FDA-356h under the "Pediatric Use" part of item 8, and also under item 20, "Other." Under "Other," the applicant should identify the location (volume and page number) of the waiver documentation in the NDA or BLA submission.

Decisions to waive the requirement for submission of pediatric assessments that are made early in the pre-approval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings) reflect the Agency's best judgment at that time. If, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision. A waiver decision becomes final once issued in the approval letter for an NDA, BLA, or supplement.

C. What Is a Deferral?

A deferral acknowledges that a pediatric assessment is required, but permits the applicant to submit the pediatric assessment after the submission of an NDA, BLA, or supplemental NDA or BLA. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all of the pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product for adult use (section 505B(a)(3) of the Act).

D. How to Apply for a Deferral

1. Criteria for Deferral (Section 505B(a)(3) of the Act)

FDA may defer the timing of submission of some or all required pediatric studies if it finds one or more of the following:

- The drug or biological product is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).

- Pediatric studies should be delayed until additional safety or effectiveness data have been collected (section 505B(a)(3)(A)(ii) of the Act).

OR

- There is another appropriate reason for deferral (section 505B(a)(3)(A)(iii) of the Act) (e.g., development of a pediatric formulation is not complete).

In addition, to obtain a deferral the applicant must submit certification of the reason(s) for deferring the assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time (section 505B(a)(3)(B)(i)-(iii) of the Act).

2. Information in a Deferral Request

FDA has provided a sample Deferral Request checklist to assist applicants in providing sufficient information for FDA to determine whether to grant a deferral request (Attachment B). To request a deferral, we recommend an applicant provide:

- Product name, applicant name, and indication
- Age group(s) included in deferral request
- Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request (e.g., studies have already been completed in other age groups and need not be deferred)
- Reason(s) for requesting a deferral
- Evidence justifying that the proposed product meets the criteria for deferral of the pediatric assessment requirement
- Description of planned or ongoing studies
- Evidence that planned or ongoing studies are proceeding
- Projected date for the submission of the pediatric assessment (deferral date)
- Applicant certification

3. Deferral Decision

The decision to defer and the deferral date will be determined on a case-by-case basis. Considerations used in determining whether and how long to defer submission of the pediatric assessment may include:

- The need for the drug or biologic in pediatric patients
- Availability of sufficient safety data to initiate pediatric trials
- The nature and extent of pediatric data needed to support pediatric labeling
- The existence of substantiated difficulties in enrolling patients
- Evidence of technical problems in developing pediatric formulations

As discussed in section V.A, the meeting minutes or a separate letter will document the deferral of pediatric assessments agreed to at the end-of-phase 2 meetings. For a deferral granted during the pre-approval development period, it is possible that FDA may reevaluate the length of the deferral closer to the time of approval, taking into account any new information obtained while the product was in development and information reviewed in the NDA or BLA. The pediatric assessments deferred under PREA are required postmarketing studies subject to the annual status

reporting and information disclosure provisions of 21 CFR 314.81(b)(2)(vii)(a) and (b) and 21 CFR 601.70.

VII. COMPLIANCE WITH PREA

If a pediatric assessment or a request for approval of a pediatric formulation is not submitted by an applicant in accordance with the statutory requirements, the drug or biological product may be considered misbranded solely because of that failure and subject to relevant enforcement action (section 505B(d)(1) of the Act). The failure to submit a pediatric assessment or request for waiver or deferral will not be the basis for withdrawing approval of a drug under section 505(e) of the Act or the revocation of a license for a biological product under section 351 of the PHSA (section 505B(d)(2) of the Act). However, the Agency could bring injunction or seizure proceedings if a product is found to be misbranded under these provisions.[8]

VIII. PREA AND PEDIATRIC EXCLUSIVITY

It is the Agency's policy to offer applicants the opportunity to qualify for ***pediatric exclusivity*** under section 505A of the Act for studies required and conducted under PREA. Under that policy, however, FDA will not issue a Written Request for or grant pediatric exclusivity for studies that have been submitted to the Agency before the Written Request is issued. Therefore, an applicant seeking to qualify for pediatric exclusivity should obtain a Written Request for studies from FDA before submitting the pediatric studies to satisfy PREA. (Note that for marketed drugs and biological products, the Agency is required to issue a Written Request prior to requiring studies under PREA (section 505B(b)(3) of the Act)). To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of PREA must also satisfy all of the requirements for pediatric exclusivity under section 505A of the Act (see sections 505A(d) and 505A(h) of the Act).

In addition, there is a noteworthy distinction between the scope of the studies requested under the pediatric exclusivity provisions and what is required under PREA. For pediatric exclusivity under the Act, FDA's authority to issue a Written Request extends to the use of an active moiety for all indications that occur in the pediatric population, regardless of whether the indications have been previously approved in adults or approval for those indications is being sought in adults (see section 505A(a), which refers only to "information relating to the use of a new drug in the pediatric population"). Under PREA, on the other hand, a pediatric assessment is required only on those indications included in the pending application (section 505B(a), which addresses "the safety and effectiveness of the drug or biological product for the claimed indications"). To learn more about eligibility for pediatric exclusivity, applicants should consult the guidance for industry entitled *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*[9] or should contact the relevant review division.

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[8] See section 302 of the Act (21 U.S.C. 332), Injunction Proceedings; section 304 of the Act (21 U.S.C. 334), Seizure.

[9] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

IX. ADDITIONAL INFORMATION

A. Additional Information Concerning PREA

General information about complying with PREA can be obtained from the Division of Pediatric Drug Development (DPDD), 301-594-7337 or 301-827-7777, e-mail pdit@cder.fda.gov. Additional pediatric information is available at http://www.fda.gov/cder/pediatric.

Specific information about the types of pediatric studies that must be conducted and requirements for submission of assessments for your drug product can be obtained from the appropriate review division.

B. Additional Information Concerning Pediatric Exclusivity

General information and the latest statistical information regarding pediatric exclusivity are located at http://www.fda.gov/cder/pediatric. You can also refer to the guidance for industry on *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*.

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ATTACHMENT A — SAMPLE WAIVER REQUEST

Product name:
IND/NDA/BLA number (as applicable):
Applicant:
Indications(s):
(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. Identify pediatric age group(s) included in your waiver request.

2. With regard to each age group for which a waiver is sought, state the reason(s) for waiving pediatric assessment requirements with reference to applicable statutory authority (i.e., one of the options (a)-(d) listed below — choose all that apply):
   (a) Studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed). If applicable, please check from the following list of adult-related conditions that may qualify the drug product for disease-specific waivers:

   _____ Age-related macular degeneration
   _____ Alzheimer's disease
   _____ Amyotrophic lateral sclerosis
   _____ Arteriosclerosis
   _____ Infertility
   _____ Menopause symptoms
   _____ Osteoarthritis
   _____ Parkinson's disease
   _____ Other (please state and justify)
   _____ Basal cell and squamous cell cancer
   _____ Breast cancer
   _____ Colorectal cancer
   _____ Endometrial cancer
   _____ Hairy cell cancer
   _____ Lung cancer (small cell and non-small cell)
   _____ Oropharynx cancers (squamous cell)
   _____ Ovarian cancer (non-germ cell)
   _____ Pancreatic cancer
   _____ Prostate cancer
   _____ Renal cell cancer
   _____ Uterine cancer

   (b) The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
   (c) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
   (d) Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. Please document previous attempts to make a pediatric formulation and describe reasons for failure.

3. Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met (not necessary if a 2(a) category is checked).

4. Applicant certification.

ATTACHMENT B — SAMPLE DEFERRAL REQUEST

Product name:
IND/NDA/BLA number (as applicable):
Applicant:
Indications(s):

(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request?

2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):

   (a) Adult studies completed and ready for approval
   (b) Additional postmarketing safety data needed (describe)
   (c) Nature and extent of pediatric data needed (explain)
   (d) Evidence provided of technological problems with development of a pediatric formulation
   (e) Difficulty in enrolling pediatric patients (provide documentation)
   (f) Other (specify)

3. What pediatric age group(s) is/are not included in your deferral request?

4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):

   (a) Adequate pediatric labeling exists
   (b) Studies completed in the specified age group
   (c) Requesting a waiver
   (d) Currently conducting pediatric studies that will be submitted with application
   (e) Other (specify)

5. Has a pediatric plan been submitted to the Agency?
   - If so, provide date submitted.
   - If not, provide projected date pediatric plan is to be submitted.

6. Suggested deferred date for submission of studies.

ATTACHMENT C — COMPLIANCE DATES FOR APPLICATIONS SUBJECT TO PREA

Categories of Application	Expected Date of Compliance
Application or supplement submitted between 4/1/99 and 12/3/03, no waiver or deferral was granted and no studies were submitted	Immediate unless FDA specifies later date
Application or supplement submitted between 4/1/99 and 10/17/02, studies were deferred to a date after 4/1/99, but no studies were submitted	Deferral date + 411 days
Application or supplement submitted between 10/17/02 and 12/3/03 and approved after 12/3/03, studies were deferred	Immediate unless later date is specified in deferral letter
Applications submitted after 12/3/03, studies were deferred	Date specified in deferral letter

The dates in the chart are relevant as follows:

4/1/99	The date the Pediatric Rule became effective
10/17/02	The date that implementation and enforcement of the Pediatric Rule was suspended by court order
12/3/03	The date that PREA was enacted

Guidance for Industry

Allergic Rhinitis: Clinical Development Programs for Drug Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

For questions on the content of the draft document contact Martin H. Himmel, 301-827-1050.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2000
Clin.

Guidance for Industry

Allergic Rhinitis: Clinical Development Programs for Drug Products

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane
Rockville, Maryland 20857
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U.S. Department of Health and Human Services
Food and Drug Administration
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GUIDANCE FOR INDUSTRY[1]

(Due to the complexity of this draft document, please identify specific comments by line number. Use the pdf version of the document whenever possible.)

Allergic Rhinitis: Clinical Development Programs for Drug Products

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) in designing development programs for oral and intranasal drug products for the treatment of allergic rhinitis in children and adults. The guidance addresses issues of study design, effectiveness, and safety for new drugs being developed for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).

II. BACKGROUND

Information about the pathophysiology and treatment of allergic rhinitis and its subtypes, SAR and PAR, has grown markedly in the past decade. The recommendations in this guidance are based on a careful assessment of important issues raised in the review of both adult and pediatric allergic rhinitis clinical trials and the Agency's current understanding of the mechanism of the two related disorders of SAR and PAR. The pathophysiology of SAR and PAR are very similar in terms of the chemical mediators produced and end-organ manifestations, with differences between the two entities primarily based on the causes and duration of disease. The study design issues pertaining to SAR and PAR trials are also very similar. Thus, these two categories are treated collectively in this guidance as *allergic rhinitis,* with differences in recommendations for the design of SAR and PAR trials indicated.

When finalized, this document will replace the previous *Points to Consider: Clinical Development Programs for New Nasal Spray Formulations* (January 1996). Sponsors are encouraged to discuss details of study design and specific issues relating to individual drug products with division review staff prior to conducting clinical trials.

Allergic rhinitis includes both nasal and non-nasal symptoms. The main nasal symptoms of allergic rhinitis are nasal itching (i.e., nasal pruritus), sneezing, rhinorrhea, and nasal congestion. Nasal pruritus and sneezing are induced by sensory nerve stimulation, whereas congestion

[1] This guidance has been prepared by the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on clinical trial design of seasonal and perennial allergic rhinitis studies in adults and children. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

results from vasodilation with resultant engorgement of cavernous sinusoids. Rhinorrhea can be induced by increased vascular permeability as well as direct glandular secretion. Important non-nasal symptoms commonly associated with allergic rhinitis include eye itching, eye tearing, itching of ears and/or palate, and eye redness.

A growing number of chemical mediators are believed to contribute to allergic rhinitis. They include histamine, leukotrienes (LTC_4, LTD_4, and LTE_4), kinins, prostaglandins, chemotactic factors, neuropeptides (e.g., substance P, CGRP, VIP), interleukins -1, -5, -6, -8, and tumor necrosis factor-α. Additional mediators with a potential role in allergic rhinitis will likely be identified in the future. Despite different causes and temporal patterns of disease, the same groups of chemical mediators appear to be regulators of the responses in seasonal and perennial allergic rhinitis. It is for this reason that distinctions between SAR and PAR in terms of clinical trial design will be made only in clinically relevant areas.

III. OVERALL CONSIDERATIONS – ADULT PROGRAM

A. New Molecular Entity

1. Number of Trials

For approval of a new molecular entity in adult and adolescent patients (age 12 years and older), at least two adequate and well-controlled phase 3 clinical trials are recommended to support either the SAR or PAR indication. Alternatively, a sponsor can submit one SAR and one PAR trial in support of both the indications, if both trials are adequate and well-controlled phase 3 trials and both trials demonstrate the safety and effectiveness of the drug for the indications.

2. Dose

The dose-response relationship for the new drug should be evaluated in these trials. These trials, or other supporting trials, should identify a *lowest effective dose* for the drug (i.e., the lowest dose that demonstrates a statistically significant difference between the to-be-marketed drug and the placebo). This recommendation is particularly important for intranasal corticosteroids.

3. Safety Monitoring

These trials should also address safety concerns, such as monitoring for adverse events, performing routine laboratory tests (i.e., blood chemistry, liver function tests, complete blood count with differential), urinalyses, and electrocardiograms, as appropriate. For SAR and PAR phase 3 trials, routine laboratory tests should be obtained in study patients at least at the initial screening and at the last visit.

For some allergic rhinitis drugs (particularly drugs in the antihistamine class), part of the safety program should include a thorough cardiac safety evaluation, with studies performed in both men and women. A suggested approach would include:

- Screening and end-of-treatment ECGs, including a careful assessment of the QT_c interval and any T wave abnormalities, as read by a ECG reviewer blinded to study treatment.

- Human dose escalation studies that evaluate serial ECGs at drug exposures up to dose-limiting toxicity of any organ system.

- For drugs metabolized by the cytochrome P450 3A4 system, drug interaction studies performed with both a macrolide and azole antibiotic.

- 24-hour Holter monitoring performed before, during, and, as appropriate, on completion of the efficacy trials for allergic rhinitis drugs suspected to have an effect on QT_c intervals from previous studies.

In addition to the studies described above, case report forms and study reports should include a detailed description of all serious cardiac adverse events and pertinent ECGs.

Sponsors are encouraged to contact the review division regarding appropriate cardiac safety monitoring for their respective drug development programs.

For many allergic rhinitis drugs, some assessment of the degree of sedation compared to the placebo should be provided in the safety database. This should primarily be based on individual patient adverse event reports of sedation and/or drowsiness (or similar terminology, as defined by the sponsor's adverse event dictionary).

Generally, long-term safety data should include at least 300 patients evaluated for 6 months and 100 patients evaluated for 1 year. The overall patient database should include at least 1500 patients. (See the International Conference on Harmonisation guidance on the *Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions* (March 1995).)

4. Corticosteroid Issues

Important safety issues for intranasal corticosteroids that would ordinarily be addressed in the adult clinical program include:

- Assessment of adrenal function using either timed urinary free cortisol level measurements (i.e., 12-hour or 24-hour), or 24-hour plasma cortisol AUC levels pretreatment and after at least 6 weeks post-treatment with study medication. A placebo and an active control (e.g., oral prednisone) should be included in these studies.

- Evaluation for possible cataract formation by slit-lamp examination, pre- and post-treatment.

- Evaluation for glaucoma, using intra-ocular pressures monitored pre- and post-treatment.

B. Change in Formulation and/or Device

1. Oral Formulations

For a change in an oral dosage form from an approved oral formulation to a new oral formulation of the same drug substance, an alternative to conducting the new molecular entity program described above is to demonstrate bioequivalence between the two formulations. This is based on pharmacokinetic comparisons (e.g., AUC, C_{max}, C_{min}) between the approved and to-be-marketed formulations. This equivalence approach allows the indications and patient populations for the new formulation to be the same as those described in the labeling of the approved product. If a significant new excipient, not previously administered at comparable levels to humans, is present in the new formulation, or if the tolerability of the new formulation is otherwise in question, short- and possibly long-term safety data may still be important for patients receiving the new formulation, even if bioequivalence is demonstrated. Additional safety and efficacy trials may be necessary to support a new formulation if bioequivalence is not demonstrated.

2. Topical Nasal Formulations

For changes in formulation and/or device for a topical nasal product (e.g., aqueous pump, spray), one of two approaches can be used to demonstrate the safety and effectiveness of the new drug product: (1) establishment of comparability between the new and previously approved (reference) formulation, or (2) development of the new formulation and/or device by a usual program for a new drug product (i.e., *stand-alone approach*).

- Comparability Approach

To demonstrate clinical comparability between the new and reference formulations, comparison of the dose-response curves of these two formulations in a single

efficacy and safety trial is recommended. Two doses of each formulation, in addition to placebo, are desirable for dose-ranging determination. The dose-ranging study should be designed to permit determination of how doses of the new formulation compare to the approved doses of the reference formulation with regard to onset of action and effectiveness. Comparative pharmacokinetic (PK) measurements (C_{max}, T_{max}, and AUC) should be included in this trial, as appropriate and technically feasible. If the reference formulation is indicated for both SAR and PAR, the dose-ranging trial can be performed in patients with either SAR or PAR (see section V of this guidance, Protocol Issues and Elements, for recommended trial durations). If the reference formulation is approved for indications in addition to SAR and/or PAR (e.g., nasal polyps or nonallergic rhinitis) no additional studies are needed to support the same indications for the new product, if comparability, as described above, is well established between the new and reference formulation.

- Stand-Alone Approach

An alternative approach or *stand-alone approach* for evaluating a topical nasal drug product with a formulation change could be a single, dose-ranging, placebo-controlled efficacy and safety trial of the new formulation in patients with either SAR or PAR. A single dose of the reference formulation as a positive control is recommended. Demonstration of effectiveness for either of these two clinical indications would allow labeling to include efficacy for both, if the reference formulation already had labeling for both. If additional indications (e.g., nasal polyps and nonallergic rhinitis) previously approved for the reference formulation are sought for the new formulation, a single clinical trial for each additional indication is recommended. Furthermore, as with the *comparability approach*, determination of the pharmacokinetics of the drug is recommended during the stand-alone approach and can be performed during the efficacy trial, if feasible.

3. Safety Monitoring

For both oral and topical nasal formulation programs described above, safety monitoring should be included for the duration of the trials. This would include evaluation of adverse clinical events, routine laboratory tests (i.e., blood chemistry, liver function, complete blood count with differential), urinalysis, and ECGs, as appropriate.

In either of these formulation programs, demonstration of long-term safety may still be important, if new inactive ingredients have been added that could affect safety, or if the new formulation and/or device results in higher systemic exposure to active ingredients compared to the approved product. In addition, if pharmacokinetic data for the formulations are not feasible, long-term safety data for the new formulation may be recommended. If necessary, long-term safety may be established by

documenting exposure of at least 200 patients to the new formulation for 6 months at the dosage proposed for marketing. Due to the duration, these studies are generally conducted in patients with PAR. An active control arm, consisting of a single dosage level of the reference formulation, is recommended. Symptom-guided dosage adjustment by study patients during the long-term open label study should be avoided, as this complicates analysis of the safety data. To minimize dropouts and to address ethical considerations, stratification of patients and dosage according to symptom severity is acceptable at the start of the open label study. However, a sufficient number of patients who receive the highest dose proposed for marketing should be included. Rescue medication should not include other intranasal drugs or intranasal products.

4. Corticosteroid Issues

For corticosteroids, if the new formulation causes higher systemic exposure to the drug substance than other formulations (either intranasally or orally inhaled) already marketed or under development for which an adequate assessment of HPA axis effects has been conducted, or if pharmacokinetic data on these other formulations is unavailable, an evaluation of the effect of the new formulation on the HPA axis is strongly recommended. For HPA axis evaluation, measurement of timed (12- or 24-hour) urinary free cortisol levels or serum cortisol AUC before and after 6 weeks of treatment are the preferable methods of assessment. If the sponsor plans to claim comparability between the reference and new formulations, and a pharmacokinetic comparison of the two products is not available, comparison with the highest marketed dose of the reference formulation is recommended.

For a change in a device, data on the performance and reliability of the new device over the period of intended use may need to be provided.

IV. OVERALL CONSIDERATIONS – PEDIATRIC PROGRAM

A. New Molecular Entity or New Pediatric Indication

The pediatric age ranges proposed for a drug product, particularly for very young patients, should be justified by the sponsor based on the presence of disease and the need for treatment in that age group. Drugs indicated for the treatment of allergic rhinitis are used in children below the age of 2 years; therefore, a complete pediatric program should evaluate the safety of antihistamines in children down to age 6 months. Similarly, based on clinical use experience, the safety of intranasal corticosteroids, cromolyn-like drugs, and anticholinergics should be evaluated in children down to age 2. Sponsors are encouraged to discuss the specifics of pediatric programs with the division on a case-by-case basis.

1. Drugs Not Previously Studied in Adults

For approval of a new molecular entity in pediatric patients (patients younger than 12 years), the number of studies recommended depends on whether the drug is already approved in adult patients. For a new molecular entity (NME) not previously approved or adequately studied in adults, the clinical program would be the same as that described for adults. This would include two adequate and well-controlled safety and efficacy trials along with appropriate long- and short-term safety data. For an NME intranasal corticosteroid, the performance of a growth study (possibly postapproval) is recommended in order to assess the potential of the corticosteroid to suppress growth in children.

2. Drugs Already Studied in Adults

For drugs already approved and/or adequately studied in adults but not yet studied in children, an appropriate pediatric dose should be determined. In addition, adequate short- and long-term safety information for the proposed pediatric age group should be provided. For oral formulations where a reasonable pharmacokinetic/pharmacodynamic (PK/PD) link for effectiveness has been established, PK data from children can be used to determine comparable exposure to adult patients, and therefore the appropriate pediatric dose.

For intranasal formulations, the performance of efficacy studies in pediatric patients is recommended, since plasma drug levels are not consistently detectable or reliable as measures of local bioavailability and topical efficacy.

3. Safety Data

Typically, 3 months of additional specific pediatric safety data for intranasal products and 1 month of additional safety data for oral products are recommended. These data should be collected in placebo controlled trials. However, the duration and number of pediatric patients exposed to the study drug for safety monitoring should be determined on an individual basis for each drug, based on anticipated side effects, pediatric PK data, and safety concerns.

4. Corticosteroid Issues

For intranasal corticosteroids, performance of a 6-week HPA axis study is recommended. Because of ethical concerns about the use of oral prednisone as an active comparator in adrenal response studies in children, inclusion of an oral prednisone arm in pediatric adrenal assessment studies is not typically recommended. However, inclusion of an active comparator arm (e.g., an intranasal corticosteroid approved in the pediatric population) is encouraged.

Based on recent information that intranasal corticosteroids have the potential to decrease growth velocity in children, a growth study is recommended for prepubertal children as a phase 4 commitment, if not before. If the studies are to be performed postapproval, it may be useful for a sponsor to include a knemometry study in the NDA submission to provide some PD growth data for consideration during the initial review. Growth studies should evaluate growth before and after treatment with the intranasal corticosteroid, using stadiometry to assess growth. Such a growth study should enroll patients with allergic rhinitis, incorporate a run-in period, and be placebo controlled. Sponsors should ensure that an adequate sample size is studied and that there is a reasonable duration of treatment (ordinarily 1 year). These recommendations allow for a better estimate of the decrease in growth velocity seen in association with intranasal corticosteroid use. Information on a clinically significant change in growth derived from knemometry studies should not be used to determine the expected change in growth velocity for longer-term studies that use stadiometry to measure growth. This is because of the nonlinearity of growth and differences in study durations for these two techniques. Sponsors are encouraged to discuss the details of their pediatric growth study design with the review division.

B. Change in Formulation and/or Device

In situations where a sponsor has conducted a change in the formulation and/or device comparability program in adults, as described above, additional pediatric efficacy studies may not be required if:

- The safety, efficacy, and PK of the new formulation are comparable to that of the reference formulation in adults, and

- The reference formulation has been approved for use in an appropriate pediatric age range.

However, depending on the specific changes that were made in the formulation and/or device, additional safety and/or use studies in children may be needed.

V. PROTOCOL ISSUES AND ELEMENTS

A. Trial Design

In the development programs of allergic rhinitis drugs, otherwise well-designed and well-conducted studies may occasionally fail to show effectiveness. This is due in part to the subjective nature of the assessments and spontaneous variability in the disease. This observation makes the use of a placebo control of paramount importance, since a

positive-control equivalence trial cannot be interpreted in such a situation. If the intent is to show that the new product is significantly more effective than an approved active control, a positive-control study may be sufficient.

The following are general recommendations on trial design for phase 3 allergic rhinitis (SAR and PAR) trials in adults and adolescents (older than 12 years) and children (younger than 12 years).

- These studies should be double-blind, placebo-controlled, and parallel group, preferably with a placebo run-in period.

- Inclusion of an active control arm is recommended for both reformulation programs (as described above) and for new drug development programs. For the new drug development program, the positive-control study is helpful in interpreting trials in which there is not a demonstrable difference between the test drug and the placebo.

- The duration of the double-blind treatment period should be at least 2 weeks for SAR trials and 4 weeks for PAR trials.

- For SAR trials, the study protocol should discuss plans for measuring pollen counts at the different study centers. The study report should document the exposure of patients to the relevant allergens during the study period. It may also be helpful to collect data on the number of rainy days during the trial and the extent of patient exposure to outdoor air.

- For SAR trials, randomization of patients within each center into the double-blind portion over a short time period (e.g., 3-4 days) is encouraged, as this generally reduces variability in allergen exposure.

- Many patients with PAR may have concomitant SAR. Therefore, PAR trials should be conducted during a time when relevant seasonal allergens are less abundant and therefore less likely to influence results of the trial (i.e., late fall and winter).

B. Inclusion Criteria

- For SAR effectiveness trials, patients should have a history of SAR for a minimum of 2 years before study entry. Documentation of sensitivity by positive skin testing (by prick or intradermal methods) or by adequately validated in vitro tests for specific IgE (e.g., RAST, PRIST) to the relevant seasonal allergen for the geographic area of the study within 12 months prior to enrollment is recommended. A positive skin test is generally defined as a wheal $\geq$ 3 mm larger than the diluent control for prick testing or $\geq$ 7 mm larger than the diluent control for intradermal

testing. Positive in vitro tests are determined by the standards of the individual reference laboratory.

- For PAR effectiveness trials, allergy to perennial allergens (e.g., dust mites, cockroaches, cats, dogs, molds) should be demonstrated in study patients by prick or intradermal skin testing (using the criteria for positivity above) or by adequately validated in vitro tests for specific IgE (e.g., RAST, PRIST). These tests should be done during the 12 months before enrollment. The patient should have a relevant allergy history to the tested allergen.

- For approximately 1 month preceding enrollment in the study, patients should not start immunotherapy or have a change in dose, and they should maintain the same dose throughout the trial.

Patients enrolled in treatment studies (as opposed to prophylaxis studies) should be experiencing symptoms meeting or exceeding an appropriate minimum level at the time of study enrollment. This could be ensured by assessing the severity of the symptoms for the primary endpoint and requiring at least moderate severity for all or the majority of individual symptoms, as defined by the study's symptom scoring scale.

C. Exclusion Criteria

The following conditions should exclude possible study participants:

- Asthma, with the exception of mild intermittent asthma (see the 1997 NAEPP guideline on asthma severity criteria), to lessen confounding by asthma medications

- Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, and/or potent or super-potent topical corticosteroids

- Use of long-acting antihistamines

- Prohibited medications or inadequate washout periods (for certain classes of medications). The following washout periods are generally sufficient:

  Intranasal or systemic corticosteroids (1 month)
  Intranasal cromolyn (2 weeks)
  Intranasal or systemic decongestants (3 days)
  Intranasal or systemic antihistamines (3 days)
  Loratadine (10 days).

- Documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator

- Chronic use of concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of the study medication

- A history of hypersensitivity to the study drug or its excipients

- Rhinitis medicamentosa

- Presence of ocular herpes simplex or cataracts (for intranasal corticosteroid trials), or a history of glaucoma (for intranasal corticosteroid or anticholinergic trials)

- Planned travel outside the study area for a substantial portion of the study period by potential participants

D. Blinding

Because allergic rhinitis trials are based on subjective endpoints, blinding is a critical consideration. Blinding to study medication should be carefully described in the study protocol (i.e., description of how the product is masked). If double-blinding is not possible, a rationale for this should be provided, along with a discussion of the means for reducing or eliminating bias. For nasal inhalers or pumps, a description of differences in appearance between active and placebo treatments should be provided in the protocol (e.g., differences in the device or in the odor or characteristic of the formulation) to help determine the adequacy of the study blind.

E. Formulations and Dosage Regimens

For all classes of allergic rhinitis drugs, sponsors are encouraged to provide information in the clinical study protocol on the specific formulations used for both the to-be-marketed drug and the placebo, along with a description of the dosing regimen. The study report should discuss whether the studied formulation was the to-be-marketed product, and if not, how the safety and effectiveness of the studied formulation will be bridged to the to-be-marketed formulation. If *bridging* of one formulation to another is proposed, information about the formulation composition and study lots should be included in the study reports for the respective products.

F. Evaluation

1. Assessment of Patient Compliance

Information about how compliance with medication use will be determined and documented throughout the trial and how noncompliance and/or missing data will be dealt with, either in the form of patient exclusion or exclusion of data points (e.g., use of

last visit data carried forward) should to be provided in the study protocol and the study report.

2. Assessment of Rescue Medication Use

If rescue medications are allowed during the study, documentation should be provided in the study protocol on how rescue medication use will be analyzed in the different treatment groups. In the clinical trial report, a section presenting rescue medication use in the different study medication groups should be provided.

3. Rating System

The preferred measures of effectiveness in allergic rhinitis trials are patient self-rated *instantaneous* and *reflective* composite symptom scores. These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, rated on a 0-3 scale of severity. Addition of non-nasal symptoms to the composite score might be pertinent for certain drug products, such as systemically active antihistamines, and should be discussed with the division on a case-by-case basis. Exclusion of symptoms from the composite score may be allowable, based on the drug's mechanism of action (e.g., exclusion of nasal congestion for antihistamines). While both patient self-rated symptom scores and physician-rated scores can be measured, the patient-rated scores are preferred as the primary measure of effectiveness.

A common allergic rhinitis rating system that has been used in clinical trials is the following 0-3 scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Regardless of the scoring system chosen, a detailed description of the symptom rating scale should be provided to patients. This should include instructions on proper completion of the symptom diary and definitions of the different categories in the scale.

4. Recording Scores

Patients should record scores in a diary at least as often as the daily dosing interval. Collection of both *reflective* symptom scores (i.e., an evaluation of symptom severity

after a predefined time period such as 12 hours) and *instantaneous* symptom scores (i.e., an evaluation of symptom severity immediately before the next dose) is recommended. Reflective symptom scores assess the overall degree of effectiveness over a prespecified time interval, whereas instantaneous scores assess effectiveness at the end-of-dosing interval.

VI. DATA ANALYSIS ISSUES

A. Collection of Data

Symptom scores should be collected at baseline and daily over the course of the trial. Collection of baseline symptom scores over several days immediately preceding patient randomization will permit the evaluation of baseline comparability of the various treatment arms, as well as the determination of treatment effects over time.

An appropriate primary efficacy endpoint is the change from baseline in the total nasal symptom score (TNSS) for the *entire* double-blind treatment period (2 weeks for SAR and 4 weeks for PAR). Depending on the drug class being evaluated, the TNSS is defined as a composite score of at least three of the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. Inclusion of nasal congestion in the TNSS may be appropriate for an intranasal corticosteroid or a decongestant, but may not be for an antihistamine, anticholinergic, or cromolyn-like agent.

When designing allergic rhinitis protocols, sponsors are encouraged to provide the value of a clinically meaningful change in the primary efficacy endpoint and the basis for this value. The statistical section of the protocol should also discuss powering of the trial based on this relevant change.

In addition to evaluating the effectiveness of the drug over the entire double-blind period, additional data presentations are helpful in evaluating the effectiveness of the drug. These include:

- Presenting the a.m. and p.m. symptom scores separately for both the reflective and instantaneous symptom assessments.

- Presenting effectiveness data for the first few days of the trial separately for both the reflective and instantaneous symptom assessments. This data presentation should also separate the a.m. and p.m. scores. This allows some assessment of the onset of action.

- Presenting the efficacy data for each week individually for both the reflective and instantaneous symptom assessments. This allows determination of both the onset of action and the durability of the response over the course of the clinical trial.

Additional secondary efficacy analyses may include the individual patient-rated symptoms that comprise the total symptom complex for the reflective and instantaneous symptom assessments for both a.m. and p.m. In addition, other patient-rated symptoms and all physician-rated symptoms can be included as secondary efficacy endpoints.

B. Time to Maximal Effect

The time to maximal effect for an allergic rhinitis medication is the earliest time (days, weeks) that the primary efficacy endpoint demonstrates the greatest numerical difference from the placebo in change from baseline. Sponsors are encouraged to include frequent symptom measurements to determine when patients may expect to see the greatest benefit from use of the drug.

C. Duration of Effect (End-of-Dosing Interval Analysis)

Evaluation of the duration of effect, as measured by instantaneous symptom scores at the end of the dosing interval, is highly encouraged to assess the appropriateness of the dosing interval. A sponsor should demonstrate, as part of the drug development program, a significant difference between drug and placebo at the end of the dosing interval.

D. Onset of Action

The definition of the onset of action of an allergic rhinitis drug is the point at which patients might reasonably expect to see a meaningful decrease in their allergic rhinitis symptoms. Statistically, it is the first time point after initiation of treatment when the drug demonstrates a change greater than the placebo treatment from baseline in the primary efficacy endpoint. This statistically significant difference between drug and placebo should be maintained for some period from this point onward.

Because onset of action information in labeling may be used as a superiority claim, at least two studies are recommended to support a particular onset of action claim. (It is useful to assess onset of action during development, regardless of any proposed claims). The two trials do not have to be identical in design, nor do they have to evaluate both SAR and PAR. Since onset of action is in large part a pharmacodynamic issue, a number of different study types could be used. Following are three study types that have been used.

- Standard phase 3 allergic rhinitis efficacy trials in which symptom scoring data are collected frequently for the first few days

- A single-dose, parallel group, placebo-controlled study of patients in a *park setting* in which patients are exposed to relevant outdoor seasonal allergens and, following dosing, have nasal symptoms evaluated on an hourly basis

- An inhalation chamber study (also known as environmental exposure unit or EEU) in which previously asymptomatic patients are exposed to a relevant allergen (generally a seasonal allergen, such as ragweed) in a controlled indoor setting and, following dosing, have their nasal symptoms evaluated on an hourly basis

Onset of action data can come from any of these three study types. However, if EEU and/or park studies are used to support an onset of action claim shorter than the onset of action seen in the phase 3 trials, these results should be replicated. This is due to the shorter duration of these trials and the restricted setting and manner in which they are conducted. In any case, information about onset of action derived from the phase 3 trials used to support approval should be included in the proposed package insert along with any data from park or chamber studies, to reflect the real world setting of the treatment trials.

VII. SAR PROPHYLAXIS TRIALS

Many variables should be considered in designing adequate prophylaxis trials for seasonal allergic rhinitis. Some of the issues that should be considered include:

- The recruitment of patients who are asymptomatic or have only mild rhinitis symptoms at baseline

- The optimal duration of pretreatment with study drug

- The difficulty in capturing the peak of the allergy season or a time when pollen counts are at their highest

- The advantages of pretreatment and/or prophylactic therapy versus treatment at the time of symptoms

Sponsors who choose to conduct prophylaxis studies should propose a minimum duration of drug exposure prior to anticipated allergen exposure and should carefully discuss the study design for each drug product with the division before initiating such studies.

Performance of an EEU study may address the adequate prophylaxis period for a seasonal allergen. However, a prophylaxis claim should be based in part on standard allergic rhinitis trial settings.