Guidance for Industry

The Content and Format for Pediatric Use Supplements

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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CLIN 1

GUIDANCE FOR INDUSTRY[1]

CONTENT AND FORMAT FOR PEDIATRIC USE SUPPLEMENTS

I. INTRODUCTION

In a final rule published in the Federal Register on December 13, 1994, FDA revised the "Pediatric Use" subsection of the labeling for human prescription drugs to provide for the inclusion of more complete information about the use of a drug or biological product in the pediatric population [21 CFR 201.57 (f)(9)]. As a result, many application holders are proposing changes in their labeling under 21 CFR 314.70 or 601.12. This guidance document discusses the content and format of these pediatric use supplements. Under the rule, FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and effects of the drug are sufficiently similar in adults and the pediatric population to permit extrapolation from the adult efficacy data to pediatric patients. The agency encourages sponsors to cooperate and work together in supporting this conclusion for drugs that are in the same class and are used for the same disease or disorder.

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[1]This guidance has been prepared by the Pediatric Subcommittee of the Medical Policy Coordinating Committee (MPCC) of the Center for Drug Evaluation and Research (CDER) in collaboration with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on pediatric use supplements. For additional copies of this guidance, contact the Division of Communications Management, HFD-210, Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-1012) or the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448. An electronic version of this guidance is also available via Internet using FTP, Gopher or the World Wide Web (WWW). For FTP, connect to the CDER anonymous FTP server at CDVS2.CDER.FDA.GOV and change to the "guidance" directory. For Gopher, connect to the CDER Gopher server at GOPHER.CDER.FDA.GOV and select the "Industry Guidance" menu option. For WWW, connect to the FDA Home Page at WWW.FDA.GOV and go to the CDER section. The document can also be obtained via a "bounce back e-mail" using the following address: GDEPED@a1.CBER.FDA.GOV and via Fax by calling the CBER Voice Information System at 1-800-835-4709.

II. CONTENT AND FORMAT

The following information should be included in the supplement in the order shown.

A. Labeling

1. Draft revised labeling

2. A marked-up copy of the current labeling, clearly showing all additions and deletions, with annotations of where the supporting data are located in the submission.

B. The paragraph(s) under which the labeling is being revised [i.e., which section of 201.57(f)(9) (ii through viii)], and a justification for the choice of that paragraph;

C. If the changes in labeling fall under 201.57(f)(9)(iv), a basis for the agency to conclude that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation of efficacy data in adults to pediatric patients;[2]

The basis should include:

1. What is known about the course of the disease in adult patients

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[2]The agency recognizes that the determination of whether a drug should qualify for "Pediatric use" under §201.57(f)(9)(iv) may be relatively simple or, in some cases, difficult and that this determination is a matter of medical judgment. In general, it will be easier to conclude that the "course of the disease and the drug's effects" are similar in the pediatric and adult populations for drugs used for acute and brief disorders or situations than for drugs used chronically or for a disorder with a lengthy and variable natural history. Factors the agency may consider in making this determination include experience with a drug or similar drugs in the same disease or in other diseases, the extent of knowledge of the pathophysiology and natural history of the disease in adults and the pediatric population, knowledge of physiology, and knowledge of a drug's metabolism and mechanism of action.

Although the pediatric population has the basic physiological processes and mechanisms for handling drugs common to all other humans, a specific study of a drug in the relevant age category should be conducted where major differences exist, e.g., different metabolites are formed. Neonates, for reasons of different physiology and of special diagnostic challenge, are the pediatric population most likely to require specific clinical effectiveness and safety data.

Specific examples for which the agency has determined that the course of the disease and the effects of the drug are similar in adults and in the pediatric population include ibuprofen, a non-steriodal anti-inflammatory drug for pain; ondansetron, for nausea and vomiting from cancer chemotherapy; and AZT, for AIDS.

and pediatric patients, and how the course is similar or different; and

2. Information on the ways the effects of the drug (both beneficial and adverse) are expected to be similar or different between adult and pediatric patients. Critical references should be included.

D. The age categories (i.e., neonates, infants, children, adolescents) for which pediatric data are being submitted;

As defined in the preamble to the final rule [59 FR 64242] the following terminology should be used:

- neonates - birth up to one month;
- infants - one month up to 2 years of age;
- children - 2 years up to 12 years; and
- adolescents - 12 years up to 16 years.

E. Identification of the kind of pediatric data submitted (i.e., pharmacokinetic/ pharmacodynamic, efficacy, safety) within each age category. This information should be submitted in a tabular format similar to that shown in Table 1 on the following page. A **check mark** should be placed in the appropriate box for which data are being submitted;

F. A summary of the information submitted to support the pediatric labeling statements and an integrated summary of the pediatric safety data with a risk/benefit assessment. The summary of safety data should include and discuss any differences from the adult population;

Table 1

TYPE OF DATA	AGE CATEGORY*			
	Neonate** (Birth up to 1 month)	Infant (1 month up to 2 years)	Children (2 years up to 12 years)	Adolescent (12 years up to 16 years)
Pharmacokinetic/ Pharmacodynamic				
- Raw data				
- Literature				
Clinical Efficacy				
- Raw data				
- Literature				
Safety/Adverse Reaction From clinical studies				
- Raw data				
- Literature				
From anecdotal reports				
- Medwatch/3500's				
- Literature				

*As defined in the preamble to the final rule (59 FR 64242).

**Premature infants - If submitting any data type in premature infants (e.g., pharmacokinetics), this should be noted and the weight groups and gestational ages studied should be defined.

III. Presentation of data

Data by type (e.g., efficacy, pharmacokinetic/pharmacodynamic, safety) should be presented, analyzed, and summarized, including data taken from published literature, using the format outlined in the "Guideline for the Content and Format of the Clinical and Statistical Sections of New Drug Applications." In presenting data, the following points should be noted.

A. The source(s) of the data should be provided. The submission should state how the medical literature was searched (e.g., Medline), the time period searched (e.g., 1990 to present), and the date(s) the search was performed. Copies of the literature referred to should be included;

B. The summary tables outlined on pages 17 and 18 of the Guideline should be included;

C. When possible, the data should be analyzed by the age categories specified in

item II. D;

D. Safety data should include the extent of exposure, duration of exposure, and adverse events. For drugs used on a chronic basis in the pediatric population, long term safety data, including data on growth and development, in particular neurofunctional development, sexual maturation, and nutrition, should be submitted;

E. The submission should include a description of the formulation(s) used and how the drug was administered (e.g., in applesauce, formula). It should state whether the marketed formulations are acceptable for pediatric use or if a new pediatric formulation would be desirable. It should state whether a pediatric formulation will be developed and, if known, the application number under which a supplement will be submitted for the formulation;

F. Any excipients in the drug product that have been shown to cause toxicity in the pediatric population should be identified, e.g., benzyl alcohol in the premature.

IV. REFERENCES

Proposed rule, 57 Federal Register 47423, October 16, 1992.

Final rule, 59 Federal Register 64240, December 13, 1994.

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