Pediatric Oncology: Written Requests and Exclusivity Determinations

April 14, 2000
Tampa, Florida

Overall Drug Development Plan - Phase 1

- A rationale for the starting dose based on either an adult dose or pre-clinical data
- A targeted study population consisting of patients who have diseases that would be likely candidates for further development. A Phase 1 study in pediatric oncology usually would enroll between 18 and 25 patients
- A plan for gathering pharmacokinetic data

Overall Drug Development Plan - Phase 1

- Definitions of the maximally tolerated dose, dose limiting toxicity, and biologically effective dose, if appropriate
- Appropriate stopping rules for toxicity
- A statistical plan based on the escalation scheme, cohort size, and stopping rules

Overall Drug Development Plan - Phase 2

- A rationale for the proposed dose
- A targeted study population consisting of patients who have diseases that would be likely candidates for further development

Overall Drug Development Plan - Phase 2

- Criteria for determining activity of the product that may lead to patient benefit. There are cases when it may not be feasible or ethical to design studies with a single drug. In such circumstances, pilot studies with combinations of drugs that are designed to demonstrate the contribution of a drug to patient benefit would be preferred
  - One example would be an add-on design where a product is added to a standard regimen compared to the standard regimen alone

Overall Drug Development Plan - Phase 2

- Appropriate stopping rules based on safety or lack of activity
- A statistical plan based on the population size, response criteria, and stopping rules. A two-phase design based on enrolling an initial cohort of patients (perhaps 14 or 15 patients) and evaluating the results prior to further enrollment may be appropriate

Overall Drug Development Plan - Phase 3

- A targeted study population that is likely to have some clinical benefit based on prior experience with the product
- A study design that will demonstrate the contribution of a product, even in combination with other products, to clinical benefit
  - One example could be an add-on design where a product is added to a standard regimen compared to the standard regimen alone

Overall Drug Development Plan - Phase 3

- Appropriate stopping rules based on safety, lack of activity, or definitive activity
- A prospective statistical plan based on the population size, response criteria, and stopping rules

Requesting Pediatric Exclusivity - Phase 1

- Must have a marketing application (approved or submitted) with patent or exclusivity that can be extended
- For some pediatric oncology drugs found too toxic in Phase 1 testing, there may not be an application to which exclusivity can attach until the adult indication application is ready for submission

Requesting Pediatric Exclusivity - Phase 1

- In such a case, FDA will provide advice upon request regarding:
  - Whether pediatric studies were conducted in accordance with and are responsive to written request
  - Whether pediatric studies were conducted in accordance with and are responsive to either a written agreement or commonly accepted scientific principles

Requests for Pediatric Exclusivity - Phase 1

- Written request may be found to be met if submitted Phase 1 study reports demonstrate unacceptable toxicity such that Phase 2 studies are no longer indicated
- Information on the unacceptability of use of product in children should be incorporated into future product labeling

Requesting Pediatric Exclusivity - Phase 2

- Ordinarily FDA will request Phase 1 and Phase 2 studies, on the assumption that
  - most products will prove safe enough to progress through Phase 2, and
  - most products for these indications would qualify for approval under Subpart E or H.
- If Phase 1 studies demonstrate acceptable level of safety, Phase 2 studies will be required to meet terms of Written Request

Requesting Pediatric Exclusivity - Phase 2

- Written Request may ask for studies with presently unvalidated surrogate endpoints
- Would lead to approval under Subpart H
- Commitment to further studies would be required; but need not be completed before pediatric exclusivity could be granted.

Sample of a Written Request for a Pediatric Oncology Drug Product Plan

---

Please refer to your Investigational New Drug Application (IND) #_____.

Background:

The Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit specific pediatric studies, detailed later in the letter. These studies investigate the potential use of {product} in the treatment of children with {specific cancer} or various cancers.

The development of pediatric oncology drugs merits special consideration. Compared to adult malignancies, pediatric cancers afflict small numbers of patients. Because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative study group. One of the highest priorities of these groups is to develop improved novel therapies. Early access to new drugs is one mechanism to achieve this goal.

Known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. Therefore, it is usually impossible to rely on pharmacokinetic and safety data alone to guide the use of these drugs in children. It is imperative that we evaluate the effectiveness and safety of new drugs in pediatric populations. In most cases, in the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA expects to be able to use flexible regulatory approaches in developing and approving drugs for pediatric tumors (e.g., basing approval on an effect on tumor size or other surrogate marker likely to predict clinical benefit (Subpart H), and/or based on safety in smaller numbers of patients (Subpart E).

The intent of designing studies for development of drugs for pediatric oncology is to proceed in the context of an overall development program. Drugs that lack dosing and pharmacokinetic information should begin with Phase 1 studies. Drugs that have dosing and pharmacokinetic data in pediatric patients should be tested in Phase 2 or pilot studies. If appropriate, a specific disease may be targeted; otherwise, several studies in a variety of tumor types, such as brain tumors, solid tumors, or hematologic tumors should be planned. Depending upon the outcome of

the Phase 2 studies, Phase 3 studies may be initiated. See the guidance for circumstances when it may be appropriate to request an exclusivity determination or advisory opinion at the end of either Phase 1 or 2.

The FDA recommends that the rationale and context in an overall pediatric oncology drug development program be included with each study

Protocols for each of your studies should be submitted to the FDA for review, but they need not be submitted simultaneously. For example, if you begin with a Phase 1 study, initially a Phase 1 protocol should be submitted for review, but the submission of Phase 2 or pilot study protocols may be deferred.

Requested studies:

Please submit information from the following types of studies:

- Type of studies: *Phase 1: A dose finding study with pharmacokinetics on 18 to 25 patients with doses determined for all appropriate age groups;*

  Phase 2 or pilot studies: Enrollment of at least 14 pediatric patients each with refractory or relapsed tumors. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

- Indication(s) to be studied (i.e., objective of each study)*:*

Refractory or relapsed pediatric malignancies

  - Age group in which study(ies) will be performed:

    Infants > 1 month of age to adolescents

  - Study endpoints:

    The pharmacokinetic study will have maximum tolerated dose (MTD) (or biologically effective dose = BED) as a primary endpoint with measurements of blood (and CSF if appropriate) concentrations, clearance, and distribution in body compartments as secondary endpoints. The Phase 2 studies or pilot studies should have a disease-specific surrogate or clinically relevant endpoint.

  - Drug information

Dosage form:

Route of administration:

Regimen: *As determined by Phase 1 study*

- Drug specific safety concerns:
- Statistical information, including power of study and statistical assessments:

  Descriptive statistics

- Labeling that may result from the study(ies):

  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- Format of reports to be submitted:

  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- Timeframe for submitting reports of the study(ies):

  Reports of the above studies must be submitted to the Agency on or before (to be determined). Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the appropriate studies to your investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports on the outcome of the studies should be submitted to a new drug application (NDA) or a supplement to an approved NDA with the proposed labeling you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of

this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if changes to this Written Request are agreed to by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you to develop additional pediatric information that may produce health benefits in the pediatric population. If you have any questions, call_____ at 301-___-____.

Back to Top Back to Pediatric Page

FDA/Center for Drug Evaluation and Research
Last Updated:May 10, 2000
Originator: OTCOM/DML
HTML by PKS