Guidance for Industry

Pediatric Oncology Studies
In Response to a Written Request

DRAFT GUIDANCE

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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)
June 2000

Clinical Medical

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U.S. Department of Health and Human Services
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Guidance for Industry[1]

Pediatric Oncology Studies In Response to a Written Request

I. INTRODUCTION

This guidance is intended to assist applicants intending to respond to a Written Request from the Food and Drug Administration (FDA) for pediatric studies for a drug that may show potential health benefits in children with cancer. The guidance will be of particular interest to applicants planning pediatric studies for which no specific oncology indication can be identified in advance (i.e., overall pediatric development studies).[2] The guidance discusses (1) the kinds of information the FDA will be asking for in its Written Requests for oncology studies, (2) the typical contents of a pediatric oncology study protocol, and (3) general requirements for studies submitted in response to a Written Request to qualify for pediatric exclusivity.

This guidance is part of the Agency's initiative to generate new knowledge to assist practitioners in the care of children with cancer and help provide pediatric patients early access to emerging new drugs.

II. STATUTORY PROVISIONS FOR PEDIATRIC EXCLUSIVITY

Section 111 of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), signed into law by President Clinton on November 21, 1997, created section 505A of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355a). Section 505A permits certain marketing applications to obtain an additional 6 months of marketing exclusivity if the applicant, in response to a Written Request, files reports of investigations studying the use of the drug in the pediatric population. The statute permits the Agency to issue a Written Request for pediatric studies under section 505A(a) or

[1] This guidance has been prepared by the Division of Oncology Drug Products of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the content and format of Written Requests for pediatric oncology studies. 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.

[2] For a more general discussion of qualifying for pediatric exclusivity, see the FDA's guidance for industry *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*.

505A(c) of the Act. A Written Request is a document in which the Agency requests an applicant to submit certain studies. The studies will be designed to provide information on the health benefits of a drug in the pediatric population.

III. WHAT IS SPECIAL ABOUT STUDYING ONCOLOGY DRUGS IN CHILDREN?

The study of oncology drugs in children merits special consideration. Compared to adult malignancies, pediatric cancers afflict small numbers of patients. Because the majority of pediatric patients receive cancer therapy as participants in clinical research protocols, participation in 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 national pediatric cooperative study groups. One of the important goals of these groups is to develop improved novel therapies, and encouraging early access to new drugs is one mechanism to achieve this goal.

Unfortunately, known and potential differences in the biology of pediatric and adult tumors make it difficult to extrapolate clinical drug effects from adults to children. As a result, it is usually impossible to rely on the pharmacokinetic and safety data gathered from studies of a cancer drug in adults to guide the use of that drug in children. Therefore, it is imperative to evaluate the effectiveness and safety of new cancer drugs in pediatric populations. To encourage applicants to study new cancer drugs in the pediatric population, the Agency is providing the following information and recommendations for applicants who receive a Written Request from the Agency for pediatric studies of oncology products.

1. In most cases, in the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA expects to use flexible regulatory approaches in approving drugs for pediatric use. Approval could be based on an effect on the size of a tumor or on another surrogate marker likely to predict clinical benefit as provided for in Subpart H of 21 CFR 314 (for drugs) and 21 CFR 601 Subpart E (for biological products). An acceptable level of safety might be demonstrated in studies of smaller numbers of patients, which could be justified under Subpart E of 21 CFR 312, which provides for flexibility in applying statutory standards of safety and effectiveness.

2. A Written Request for pediatric studies of a drug for pediatric oncology will usually be issued in the context of an overall development program for the drug. 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.

3. Because pediatric oncology drugs are usually approved on the basis of phase 2 studies[3] and, therefore, phase 3 studies for pediatric oncology drugs are generally initiated postapproval, phase 3 studies usually will not be requested in a Written Request as a prerequisite to a grant of pediatric exclusivity.

[3] See 21 CFR 312.82(b).

4. When planning pediatric protocols, applicants should discuss protocol designs with a pediatric cooperative study group. These groups have experience, expertise, and resources that can help applicants optimize their study designs and accrue patients.

IV. WHAT WILL A TYPICAL WRITTEN REQUEST ASK FOR?

To assist applicants planning to undertake pediatric oncology studies, the Agency is providing the following information on a typical Written Request for pediatric oncology studies. Applicants should also consult the FDA's guidance for industry on *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act* (September 1999), which discusses in detail the contents of Written Requests, responses to those requests, and how to qualify for pediatric exclusivity. A sample Written Request for pediatric oncology studies is available on the Internet at http://www.fda.gov/cder/pediatric/.

A. Phase 1 and 2 Studies

Because of the high toxicity of many oncology drugs and the difficulty in extrapolating efficacy and safety from adult experience to children, it is particularly difficult to predict which drugs might prove too toxic for use in pediatric patients and which warrant further study. Typically, a Written Request for pediatric oncology studies will ask for phase 1 and phase 2 studies, on the assumption that most products will prove safe enough to progress through phase 2, and on the assumption that most products for these indications would qualify for approval based on surrogate markers (Subpart H, or Subpart E for biological products) or under special conditions (Subpart E).

If the applicant submits phase 1 study reports that appear to demonstrate an ***unacceptable*** toxicity such that phase 2 studies are no longer indicated and FDA agrees with those findings, FDA will generally find that the terms of the Written Request have been met and that no further pediatric studies are required. In such cases, information on the toxicity of the product in children would be incorporated into any future labeling for the product (if the product were already approved in adults or were it to be approved later for use in adults) (see discussion under section VI). If phase 1 studies demonstrate an acceptable level of safety, phase 2 studies will generally be required to meet the terms of routine Written Requests for pediatric oncology studies.

B. Studies Using Unvalidated Surrogate Endpoints

A Written Request may ask for studies using presently unvalidated surrogate endpoints. As with other such development programs, if the data support the approval of a product for a specific indication, or indications, based on unvalidated surrogate endpoints, the product (and indications) would be approved under 21 CFR 314 Subpart H or 21 CFR 601 Subpart E. In such a case, the sponsor would have to commit to further studies as required in those regulations. However, completion of those further studies would not be required before pediatric exclusivity could be granted.

C. Study Rationale and Context

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

V. WHAT WILL TYPICAL PROTOCOLS LOOK LIKE?

The following lists illustrate what the Agency believes should be included in a typical pediatric oncology study protocol. The lists are organized by study phase.

1. Phase 1 studies

A phase 1 pediatric oncology study protocol should contain the following characteristics:

- A rationale for the starting dose based on either an adult dose or preclinical 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
- 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.

2. Phase 2 studies

A phase 2 pediatric oncology study protocol should contain the following characteristics:

- A rationale for the proposed dose
- A targeted study population consisting of patients who have diseases that would be likely candidates for further development
- Criteria for determining activity of the product that may lead to patient benefit. There are cases when it may be infeasible or unethical 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 and compared to the standard regimen alone.

- 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.

  Phase 2 studies should be considered for a range of potential indications based on consultation with pediatric oncologists.

3. Phase 3 studies

Because approval for oncology drugs will generally occur at the end of phase 2 under subparts E or H, information from phase 3 studies would generally not be included in a Written Request and would not be required for a grant of pediatric exclusivity. However, because phase 3 pediatric oncology studies are generally the postapproval *standard of care* for children with various malignancies, we have provided the general characteristics of phase 3 pediatric oncology studies, which most likely are undertaken in conjunction with a cooperative group as part of such standard of care.

- 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.

- 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.

VI. HOW DOES AN APPLICANT QUALIFY FOR EXCLUSIVITY ?

Once an applicant has responded to a Written Request by carrying out pediatric studies and submitting them to the Agency, the FDA must decide if the product qualifies for 6 months of marketing exclusivity.

A. What Requirements Must the Studies Meet?

Under section 505A, the Agency must determine that the pediatric oncology studies:

1. Were conducted in accordance with and are responsive to the Written Request

2. Were conducted in accordance with and are responsive to either a written agreement if one existed,[4] or commonly accepted scientific principles if no written agreement exists

3. Were reported in accordance with FDA's requirements for filing

B. What If Pediatric Studies Were Discontinued After Phase 1?

To obtain pediatric exclusivity under section 505A, an applicant must file the pediatric study reports to a marketing application (either approved or submitted for approval) that has either patent or other marketing exclusivity (or other potential marketing exclusivity) that can be extended by obtaining pediatric exclusivity.

In the case where a drug is found to be too toxic in phase 1 testing to continue to phase 2 (or does not show sufficient evidence of effectiveness at the end of phase 2 to warrant approval or phase 3 testing) and at the time pediatric testing is stopped no application has been filed to which the pediatric studies can be submitted, exclusivity may still be granted at the time the application for an adult indication is filed. In such a case, prior to finishing the study of the adult indication and submitting an application in accordance with FDA's requirements for filing, the applicant may want to request advice from FDA to determine if further work on the pediatric studies is needed to meet the terms of the Written Request. If an applicant requests such advice, it should submit its pediatric study reports to the appropriate IND (investigational new drug application) and submit a specific request for advice. FDA will determine if the studies satisfy the terms of the Written Request and were conducted in accordance with commonly accepted scientific principles (or a written agreement) and will so inform the applicant. However, this advice does not substitute for a pediatric exclusivity determination.

Final determination of pediatric exclusivity can only occur when the studies are submitted to an existing application or as a part of a new marketing application in accordance with FDA's requirements for filing. In all cases, pediatric exclusivity, if granted, will attach to exclusivity and patent protection listed in the Orange Book for any drug containing the same active moiety as the drug studied and for which the party submitting the studies holds the approved new drug application.[5] For studies conducted on an unapproved drug, pediatric exclusivity will attach to any exclusivity or patent protection that is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)* upon approval of that unapproved drug.[6]

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[4] Written agreements are discussed in detail in the Agency guidance *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act* (September 1999).

[5] See sections 505A(a) and (c) of the Act.

[6] For a detailed discussion of applications to which pediatric exclusivity will attach, see *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act* (September 1999).