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Pediatric Oncology: Regulatory Initiatives

STEVEN HIRSCHFELD, ALLA SHAPIRO, RAMZI DAGHER, RICHARD PAZDUR

Division of Oncology Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, USA

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INTRODUCTION

The development of pediatric oncology therapies merits special consideration. Compared to adult malignancies, the tumor biology is usually different, the incidence is much lower, and the majority of children are treated in clinical trials.

Compared to the over one million new adult malignancies diagnosed annually, an estimated 12,000-13,000 new malignancies are diagnosed in children and adolescents under the age of 20 every year [1]. Because the majority of 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 such as the Children’s Oncology Group, National Wilms’ Tumor Study Group, Intergroup Rhabdomyosarcoma Study Group, and the newly formed Pediatric Brain Tumor Consortium. One of the highest priorities of these groups is to develop improved therapies. Early access to new agents is the optimal mechanism to achieve this goal.

Known and potential differences in the biology of pediatric and adult tumors and in physiology between adults and children will usually not permit the extrapolation of clinical activity from adults to children. It therefore becomes necessary to evaluate the effectiveness and safety of new drugs separately in adult and pediatric populations.

ABSTRACT

The majority of children with cancer receive therapy as participants in clinical research protocols coordinated by national pediatric cooperative groups. One of the highest priorities of these groups is the development of novel therapies. Due to differences in the biology of pediatric and adult tumors and in physiology between adults and children, it is usually necessary to evaluate the safety and effectiveness of new drugs separately in adult and pediatric populations. To stimulate the development of new therapies for pediatric indications and encourage the submission of clinical data to support pediatric product labeling, the U.S. Food and Drug Administration has undertaken two initiatives. In 1998 the FDA issued a regulation (The 1998 Final Pediatric Rule) that mandated if a drug or biological is under review for a claim and the disease exists in both pediatric and adult populations, pediatric studies must be performed. Section 111 of the FDA Modernization Act of 1997 states that if a drug product has exclusivity based on a patent or marketing license, the exclusivity can be extended by six months for the submission of pediatric data to the FDA. The incentive applies to both approved drugs and those under development. These initiatives are intended to enhance access to new anticancer therapies and promote labeling for pediatric oncology indications. The Oncologist 2000;5:441-444
THE 1994 FINAL PEDIATRIC RULE

In 1994, the U.S. Food and Drug Administration (FDA) issued a regulation (The 1994 Final Pediatric Rule) that allowed efficacy data from adult studies to be extrapolated to a pediatric population, if the disease under study existed in both the pediatric and adult populations and the response to therapy was substantially the same [2]. The intention was to strongly encourage sponsors to develop drugs in pediatrics and provide pediatric information for drug labeling. Specifically, the provision permits the use of information from adequate and well-controlled adult studies to support a pediatric indication. However, the course of the disease and the effects of the drug must be sufficiently similar in the two populations to permit this data extrapolation from adult efficacy studies to pediatric patients. Additional pediatric information, such as appropriate pediatric dosage (e.g., pharmacokinetic data) and safety information, must also be submitted. This pediatric labeling regulation provides flexibility in the data needed for pediatric information in drug labeling. This flexibility applies to both marketed drugs and new molecular entities under regulatory evaluation. However, for a disease specific to children or different between children and adults, (as are most pediatric oncology indications), adequate, well-controlled clinical trials demonstrating safety and efficacy in the pediatric population remain necessary to register a pediatric indication.

THE 1998 FINAL PEDIATRIC RULE

Effective April 1, 1999, a new rule mandates pediatric studies if an application for a claim is under review and the proposed indication is for a disease that exists in both adults and children [3]. The pediatric studies need not be completed prior to submission of the adult data for review. There is no intent to delay regulatory review and marketing of a product for adult use to submit pediatric data. The submission of pediatric data can be deferred by request. A mechanism also exists to request a full waiver if a sponsor feels that no pediatric studies are warranted, or a partial waiver if pediatric studies in a particular population, e.g., neonates, are not warranted. The initial application of this new pediatric rule in pediatric oncology will be limited, (e.g., selected central nervous system tumors and lymphomas being potential candidate indications); however, a newly formed pediatric subcommittee of the Oncologic Drugs Advisory Committee will be examining the applicability of the 1998 Rule to adult and pediatric tumors in a systematic manner. Products with Orphan Drug designation are exempted from the 1998 Rule.

THE 1997 FDA MODERNIZATION ACT

An additional initiative meant to address the circumstance when the pediatric and adult indications are different, and enhance the incentives when the indications are the same, is Section 111 of the FDA Modernization Act of 1997 (FDAMA) [4]. If a product has exclusivity based on either a patent or a marketing license, the exclusivity can be extended by six months (up to a maximum of two times) for the submission of pediatric data to the FDA. The data must be submitted in response to a Written Request from the FDA; compliance is voluntary. The incentive does not apply to medical devices, most biologics and some antibiotics. The exclusivity extension of six months applies to the entire product line for an active moiety for the first determination, but for a second six-month extension, it is limited to a pediatric indication. The incentive applies to both approved drugs and drugs under development.

The mechanism provides that a sponsor or interested third party submits a proposal for a Written Request to the FDA. A proposal should be sufficiently detailed, providing an indication, the type of information intended for submission, and if warranted, appropriate study designs. If the FDA considers the proposal acceptable, the Agency will issue a formal Written Request that describes the required information necessary to qualify for the exclusivity extension and the time frame for data submission. The FDA may also issue a Written Request without solicitation (Fig. 1).

The general requirements of a Written Request will be to provide dosing and pharmacokinetic information in the target populations along with efficacy data in one or more specific diseases. In general, these requests will ask for early phase I studies to assess pediatric tolerability and seek potentially responsive tumors followed, if the drug is tolerated, by appropriate phase II studies in specific populations. It must

Figure 1. Steps to qualify for exclusivity extension under FDAMA.
be emphasized that studies are not limited to monotherapy, nor are monotherapy studies being proposed solely for regulatory purposes. The only justification for a monotherapy study is when there is a sound biological and ethical basis to consider such a design.

To expedite this initiative, we suggest that sponsors discuss a pediatric development plan with a pediatric cooperative study group to utilize its expertise and resources to optimize study design and patient accrual, and determine which cancers should be studied. Sponsors are encouraged to generate proposals for Written Requests in conjunction with pediatric cooperative groups prior to submission of the proposal to the Division of Oncology Drug Products.

Following receipt of a Written Request, which is a request for the type of information, a sponsor will then submit protocols to the FDA which will outline how the information will be obtained. Although it is not necessary to submit pediatric protocols for review, it is highly recommended. A Written Request may be amended at any time prior to submission of the Study Report. Examples of the type of information that may be requested in an amendment are a change in a study endpoint or an extension of the date the report is due. A Written Request is not considered amended until the FDA has issued an amended Written Request.

When the FDA receives a Study Report that fulfills the terms of the Written Request within the stipulated time frame, the results are evaluated with respect to compliance with the Written Request. If the FDA determines that the terms are met, irrespective of outcome, the exclusivity extension may be granted. The rationale for granting the exclusivity extension, even for data failing to demonstrate therapeutic efficacy, is that a well-designed and well-executed pediatric study may provide important public health information.

Because the program is voluntary, the FDA cannot require a sponsor to perform a trial or provide a drug for study, but can only present the opportunity to qualify for a financial incentive. To date, the Division of Oncology Drug Products has issued eleven Written Requests. Overall, the financial incentive offered under FDAMA has attracted much interest. As of October 1, 2000, the FDA has received a total of almost 200 proposals and issued over 150 Written Requests. Twenty-four drugs have already been granted exclusivity extensions.

**APPROVAL FOR PEDiatric INDICATIONS**

To obtain a pediatric indication as a marketing claim, data based on adequate and well-controlled trials are usually required. The FDA has taken a flexible approach with regard to the requirement for adequate and well-controlled trials, and in certain circumstances has allowed one definitive study to lead to product labeling for anticancer drugs. There are also mechanisms available to issue a conditional marketing license based on preliminary data under the Reinventing Cancer Initiatives of 1996 [5]. These are reflected in the Code of Federal Regulations and referred to as Subpart E and Subpart H [6].

In the absence of available therapy to treat refractory stages of most pediatric malignancies, the FDA expects to be able to use the regulatory approaches of Subpart H of our regulations in approving drugs for pediatric tumors, basing approval on an effect on response rate or other surrogate markers likely to predict clinical benefit, or on safety in smaller numbers of patients. If approval is based on surrogate endpoints or smaller safety numbers, subsequent further studies would usually be needed.

There is no formal linkage between qualifying for an exclusivity extension, complying with the 1998 Pediatric Rule, and receiving approval for a pediatric indication.

**CONCLUSION**

The intent of the two FDA pediatric initiatives is to stimulate the development of new therapeutics for pediatric indications and encourage the submission of quality clinical data to support pediatric product labeling. The 1998 Pediatric Rule is mandatory, applies to drugs and biologicals, but is restricted to the indication under review. The Exclusivity Extension under FDAMA is voluntary, applies only to drugs, and can apply to any pediatric disease (Table 1). In oncology, there are additional and specific goals including lowering the barrier to pharmaceutical manufacturers to initiate studies in pediatric patients, fostering collaboration between the

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**Table 1. Comparison of major features of FDAMA Pediatric Exclusivity Extension and 1998 Pediatric Rule**

<table>
<thead>
<tr>
<th>FDAMA Pediatric Exclusivity Extension</th>
<th>1998 Pediatric Rule</th>
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<tbody>
<tr>
<td>Voluntary</td>
<td>Mandatory</td>
</tr>
<tr>
<td>Applies to entire product line</td>
<td>Only applies to the product and indication under review</td>
</tr>
<tr>
<td>No restriction on eligible pediatric diseases</td>
<td>Only applies if the pediatric disease is similar to the adult disease</td>
</tr>
<tr>
<td>Only applies when there is underlying patent or exclusivity protection</td>
<td>Applies to biologicals</td>
</tr>
<tr>
<td>Biologicals and some products excluded</td>
<td>Orphan products excluded</td>
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<td>Orphan products included</td>
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National Cancer Institute-sponsored cooperative groups and pharmaceutical industry, rewarding good faith efforts to develop drugs for pediatric malignancies regardless of outcome, and examining the linkages among adult and pediatric cancers to advance the design of clinical trials.

Pediatric patients deserve the same access to new drugs and standards for product labeling as adults.

Further information on the regulatory aspects of pediatric oncology drug development may be obtained from the FDA at www.fda.gov/cder/cancer.

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