Patient Access to New Therapeutic Agents for Pediatric Cancer

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TABLE OF CONTENTS

I. PURPOSE AND SCOPE

A. Purpose

Section 15(d) of the Best Pharmaceuticals for Children Act of 2002 (BPCA) (P.L. 107-109), directed that not later than January 31, 2003, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health (NIH), must submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents. This report is submitted in accordance with that requirement.

B. Scope

For the purposes of this report, *access to investigational drugs* is defined as the ability of pediatric cancer patients to receive treatment with a drug based on a sound scientific rationale for its use in the absence of a specific Food and Drug Administration (FDA) - approved pediatric indication.

The scope of this report includes:

- access to investigational drugs through the clinical trials network
- access to investigational drugs outside of the clinical trials network
- parent, patient, and physician access to information about new drugs
- legislation designed to improve access and encourage pediatric drug development
- initiatives designed to identify and address some of the issues that hinder pediatric drug development
- challenges that NIH/National Cancer Institute (NCI) and FDA face together in further improving access and outcomes for children with cancer

Access to investigational drugs through the clinical trials network is described in the oncology community as *protocol access*, and access to investigational drugs outside of the clinical trials network is termed *non-protocol access*. *Protocol access* is defined as participation in clinical trials that are designed to investigate safety and effectiveness in

a well-defined patient population. *Non-protocol access* is defined as use of an investigational drug to treat a single patient or a group of patients who are not eligible for or who are unable to participate in a clinical trial designed to evaluate a drug's safety and effectiveness in a systematic manner. While a study plan or *protocol* may be written to ensure appropriate administration of the drug and adequate safety monitoring, the focus of a *non-protocol access* study is on the treatment of individuals, rather than on an investigation designed to further drug development.[1]

[1] Although the definitions may sometimes appear inconsistent (e.g., a *protocol* may be written for a *non-protocol access* program), these terms are widely used and understood in the oncology community. For this reason, these terms are used in this report based on the definitions provided.

II. EXECUTIVE SUMMARY

A. Summary

Although survival for pediatric cancer patients has improved steadily during the past four decades, many children still die of cancer every year, and children who are cured of cancer may be at risk for short- and long-term adverse effects of therapy. To continue to improve survival rates and address clinical outcomes for these children, it is critical to develop new, widely accessible therapies to treat pediatric cancer. An equally important area of focus is product labeling, which needs to be updated appropriately with pediatric information so that products can be used safely and effectively in this population. This report describes the collaborative efforts of NCI and FDA to help achieve these goals.

Most pediatric cancer patients have access to new therapies through enrollment in clinical trials. NCI funds a highly regarded national clinical trials program, the Children's Oncology Group (COG), as well as other, smaller consortia. Approximately 4,000 children participate in NCI-sponsored clinical trials annually, and in 2002, more than 500 pediatric patients enrolled in 50 NCI-sponsored clinical trials evaluating investigational agents. Additional trials sponsored by other funding sources (non-governmental or pharmaceutical companies) are also conducted at pediatric cancer centers. Approximately 90 percent of children with cancer are treated at COG member institutions and about one-half of that group enrolls in clinical trials, a remarkably high rate, especially given that the clinical trial enrollment rate of adult cancer patients is less than 5 percent. The high rate of participation in clinical trials for new therapies to treat pediatric cancer has been a major contributor to the improved treatment success rate in children with cancer.

For pediatric cancer patients who are unable to enroll in clinical trials, FDA and NCI have programs that permit non-protocol access to new treatments. These programs may include a study plan (protocol) to ensure correct administration of the treatment and careful safety monitoring, but these programs focus on treatment of individual patients. FDA uses single patient Investigational New Drug application (IND) submissions (for emergency or non-emergency situations) and Treatment IND protocols (one study to treat multiple patients). NCI makes treatments available outside of clinical trials through the Special Exception protocol for single patients and the Group C protocol for groups of patients. Applications are reviewed to ensure patient safety and are usually approved. Relatively few such requests are submitted for pediatric cancer patients, probably because (1) some investigational agents are accessible for pediatric patients through Phase 1 and Phase 2 protocols, (2) many potentially useful drugs are commercially available agents, (3) there is strong support in the pediatric oncology community for the clinical trial mechanism, and (4) evidence to support use of investigational agents often comes from adult cancers that do not have a pediatric correlate.

NCI and FDA have worked together to inform the public and physicians about access to investigational agents for all pediatric cancer patients, both on and off-protocol. Information services include the Clinical Trials Data Bank, the Treatment Referral Center program at NCI, and the Cancer Information Service at NCI.

Regulatory initiatives and legislation that address access include the 1998 Pediatric Rule and the Pediatric Exclusivity program. The Pediatric Rule required all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to include an assessment of the safety and effectiveness of the product in pediatric patients unless the requirement was waived or deferred (*Federal Register,* December 2, 1998*,* 63 FR 66632). The Pediatric Rule was invalidated in 2002 after a court challenge.

The Pediatric Exclusivity program, previously part of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and now incorporated in the BPCA, is a voluntary program that directs FDA to request pediatric studies from sponsors (a Written Request) to address public health needs. If a sponsor completes and submits the requested pediatric studies, the sponsor may qualify for an additional 6 months of marketing exclusivity for all products that contain the same active moiety and have existing exclusivity or patent protection. Exclusivity is granted for negative studies if the data provided fairly respond to the terms of the Written Request, because data demonstrating that a product is not effective or is unsafe in a pediatric cancer may still provide important information to patients and practitioners. FDA developed a special program for pediatric oncology Written Requests and issued a guidance for industry *Pediatric Oncology Studies In Response to a Written Request*.[2] FDA has issued Written Requests to the manufacturers of about 30 cancer products under this program. As of August 2003, four products to treat cancer have been granted exclusivity with appropriate labeling changes.

FDA and NCI continue to work together to further improve access to new therapeutic agents for children with cancer. The agencies cosponsored a Workshop on Pediatric Oncology Drug Development in July 2002 to identify issues that impede pediatric drug development and to help frame these issues for consideration by the Pediatric Subcommittee of FDA's Oncologic Drugs Advisory Committee (ODAC). These discussions resulted in the formation of new liaisons with the pharmaceutical industry and the identification of new areas of research to predict effectiveness of drugs for pediatric cancers.

New programs under development to expand access include establishment of a pediatric drug testing program at NCI and additional incentives for pharmaceutical development of promising new agents. NCI is developing a Pediatric Preclinical Testing program that will systematically evaluate new therapeutic agents against a panel of pediatric cancers growing in mice and against a panel of pediatric cancer cell lines. New agents will be tested in this system and those that demonstrate activity against

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

specific childhood cancers may be prioritized for clinical testing in children with these cancers. This program will also test pediatric tumors for gene and protein expression that could lead to the development of new targeted therapies designed to inhibit or stimulate a gene or a protein important in the development or prevention of a specific cancer. NCI also administers small business and investigator grants to biotechnology companies and academic centers to support further development of new agents to treat childhood cancers. FDA provides grants to companies and investigators developing products for orphan diseases through the Orphan Products Development program.[3]

B. Future Approaches

Pediatric patients have access to new oncology drugs primarily through participation in clinical trials. NCI, FDA, clinical investigators, and pharmaceutical sponsors throughout the country work closely together to make access to clinical trials available. Access through clinical trials provides not only patient access to treatment but also critical information that can advance the science of treating pediatric patients. The application of the results from these clinical trials is a critical factor in the notable increase in survival rates of pediatric cancer patients. Despite these successes, pediatric access to new oncology drugs can be improved. NCI and FDA, working together in the Department of Health and Human Services, have identified the following approaches to improving access:

- Reliable prioritization of the best potential agents for clinical testing in children with different types of cancer through systematic evaluation of new agents in childhood cancer preclinical models. NCI's Pediatric Preclinical Testing Program will contribute to this aim but will need the support of pharmaceutical sponsors to meet its objectives. New preclinical models of childhood cancers may also be needed to better identify new agents that should be tested in children.

- Further research into the biological mechanisms of pediatric tumors. This type of research might improve the development of new therapies by identifying biologic mechanisms common to adult and pediatric tumors, encouraging earlier testing in children or use in a pediatric tumor not anticipated by conventional tumor classification.

- Continued identification of products meriting a Written Request from FDA to a pharmaceutical sponsor to conduct studies and potentially qualify the product for Pediatric Exclusivity.

- Continued collaboration with the pharmaceutical industry to make new agents available for evaluation in children at an appropriate time in a drug's development.

[3] An orphan drug is intended to treat a condition affecting fewer than 200,000 people in the United States or that will not recover development costs plus a reasonable profit within 7 years following FDA approval. Further information is available at http://www.fda.gov/orphan

- Ongoing training of qualified pediatric researchers and physicians to maintain the current high level of care.

- Continued support of pediatric clinical research programs to obtain safety and efficacy information through appropriately conducted clinical trials.

By working together in these areas, NCI and FDA will continue to coordinate their resources to improve outcomes for children with cancer. Under a recently announced agreement between FDA and NCI, the two agencies will share knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. An NCI/FDA Oncology Task Force, which involves senior staff from both agencies, will oversee implementation of the specific components of the agreement.[4]

III. BACKGROUND

A. Pediatric Cancer in the United States

In the United States, approximately 12,000 new cases of cancer are diagnosed in children each year, and approximately 20,000 children receive treatment for cancer in a given year. Survival rates have steadily improved for children with cancer, from a 25 percent 5-year survival rate in the 1960s to a 78 percent 5-year survival rate for the period 1992-99. The observed improvement in survival results from several factors:

- Many childhood cancers are responsive to some form of therapy, such as surgery, radiotherapy, or chemotherapy.

- A national clinical trials network for pediatric oncology, funded by NCI, has developed these therapies systematically.

- Approximately 90 percent of children with cancer are treated at specialized pediatric cancer centers with access to advanced knowledge of best available therapy. Treatment at these centers ensures access to clinical trials for eligible children and to state-of-the art care if no trials are available.

- A high percentage of children with cancer enter clinical trials. Approximately 50 percent of children with cancer participate in NCI-sponsored clinical trials, and additional children participate in trials conducted by smaller clinical trials networks and commercial sponsors. In contrast, in adult oncology, less than 5 percent of patients enroll in clinical trials.

COG, the largest of the clinical trials networks for pediatric oncology, is comprised of researchers at 235 centers of excellence, 212 in the United States, that jointly develop

[4] Press release available at http://www.fda.gov/bbs/topics/NEWS/2003/NEW00912.html

and conduct cancer trials for children. This network system is critical to the successful development of effective treatments because relatively small numbers of children with each type of cancer are diagnosed each year Childhood cancer, in many cases, cannot be studied effectively at individual institutions. NCI provides administrative oversight for COG**,** and FDA provides regulatory oversight for the therapeutic products used in the studies. Participants in this network include patients, their families, advocates for pediatric oncology patients, pediatric cancer researchers (clinical and laboratory), health care professionals, drug manufacturers, NCI, and FDA. This cooperative study of new medicines is critical to improving survival in pediatric cancers.

Despite progress in improving outcome and survival for children with cancer, childhood cancer remains the leading disease-related cause of death in children and adolescents in North America, with about 2,300 deaths each year. More children die from cancer than from asthma, diabetes, cystic fibrosis, congenital anomalies, and AIDS combined. Many children are not cured with available therapies, and these therapies may be associated with long-term toxicity. Access to new drugs is an important component of improving survival rates. It is critical to develop new products for all cancers to (1) treat patients unresponsive to current therapy, (2) further decrease mortality, and (3) decrease short- and long-term adverse effects of therapy. Further development of promising new therapies through collaboration with the pharmaceutical industry and the childhood cancer clinical trials networks is critical to improving access to effective treatments for children with cancer.

B. The Clinical Trials Process

The pharmaceutical industry, clinical investigators, patients and their advocates, NCI, and FDA agree that the optimal means of providing patient access to new therapies for cancer is through participation in clinical trials. Clinical trials maximize the opportunity to gather and synthesize useful information about a product to benefit the entire current and future patient population. Clinical trials also provide a range of patient protections and benefits, including:

- treatment on a protocol that has undergone multiple levels of review and incorporates best available therapy
- free investigational medication, unless FDA permits cost recovery by the sponsor of the clinical trial
- careful monitoring by physicians having the most experience with the unapproved drug
- systematic collection and analysis of adverse events and efficacy endpoints
- oversight by trained professionals at many levels, including the treating physician, the principal investigator of the trial, NCI (for cooperative group trials),

FDA, the local Institutional Review Board (IRB), and, frequently, the drug manufacturer

Conduct of oncology clinical trials is generally divided into four phases:

- **Phase 1** studies are conducted in patients with advanced disease and, generally, for whom no therapy is available. The purpose of a Phase 1 study is to (1) determine dosing and preliminary safety information for investigational drugs, (2) test the use of a new drug in combination with a marketed drug, or (3) test new doses or combinations of already marketed drugs.

- **Phase 2** studies examine preliminary efficacy at the dose and dosing schedule determined in Phase 1 in specific cancer types and provide further safety information. These trials are usually single-arm studies (i.e., a single treatment regimen is studied) with a response rate endpoint (i.e., a measure of study outcome). If activity can be demonstrated in Phase 2, further clinical development proceeds in Phase 3.

- **Phase 3** studies usually compare a new treatment regimen with best available treatment to determine which is the better therapy (i.e., a controlled clinical trial). Controlled clinical trials with protocols that have undergone appropriate external scientific review have been critical in determining the most effective therapies. Congress recognized the value of such evidence-based medicine in the 1962 Amendments to the Food, Drug, and Cosmetic Act, which require "substantial evidence of effectiveness based on adequate and well-controlled clinical investigations." Adequate and well-controlled investigations are defined in the Code of Federal Regulations (21 CFR 314.126).

- **Phase 4** trials are studies performed after a drug is marketed to further define safety and efficacy.

When studying treatments for cancer, it is generally necessary to conduct separate studies with children, even if a drug has been tested and approved in adults. In the design of Phase 1 protocols, particular attention is given to dosing and pharmacology. Many cancer therapies are administered based on the calculated body surface area of the patient, but scaling adult doses to children based solely on body surface area ignores developmental differences. These differences include: (1) the proportion of fat to water in the body, which changes how a drug is distributed in children and (2) changes in organ size, maturation, and function, which affect drug metabolism and clearance. How a drug is absorbed, distributed in the body, then metabolized and excreted is known as pharmacokinetics. Advanced methods for performing pharmacokinetic studies using minimal blood volumes and number of patient samples are designed into most protocols. The minimization of blood volumes and number of samples required is particularly important in pediatric patients, who have a lower blood volume than adults and may not tolerate repeated venipuncture. There is also great interest in differences in how individual patients metabolize drugs as a result of specific

inherited genes (pharmacogenetics). These variations in pharmacokinetics and pharmacogenetics can affect the dose and dosing interval in children. Different toxicities or different severity of toxicities can occur in children compared to adults because of these variations. Consequently, Phase 1 data from adults cannot be generally extrapolated to children.

Phase 2 studies are performed in children with specific tumor types to obtain a preliminary estimate of efficacy and further safety information. Because pediatric and adult cancers frequently differ, it is often not possible to extrapolate adult efficacy results to children. Similarly, Phase 3 studies are needed to evaluate new therapies in relation to best available treatment in pediatric cancers.

The clinical trials process includes the scientific concepts of:

- combination of data from all institutions to rapidly accumulate the necessary number of patients
- use of standard criteria for diagnosis, treatment, and measurement of effect
- use of good study design with random assignment of patients to different treatment groups
- use of prespecified statistical analysis and collaborative reporting of results

This process ensures orderly, systematic evaluation of new medicines for pediatric patients and provides them with the best means of access to new therapies. FDA regulates investigational drugs by requiring sponsors to file an IND to study a drug in humans. FDA regulations provide multiple mechanisms, discussed below, to facilitate timely access to investigational drugs with appropriate protections for patients, particularly those with life-threatening diseases.

C. Current Status of Pediatric Labeling

Because surgery and radiotherapy can be used to treat only selected tumors and only relatively limited sites of disease, chemotherapy forms the cornerstone of treatment for most pediatric malignancies. Between 1948 and January 2003, FDA approved approximately 120 cancer therapies. Because of differences between adult and pediatric cancers, approximately 30 of these drugs are commonly used for children with cancer. Of these 30 drugs, only 15 have pediatric information in the approved product labeling, and this information is often limited in scope.

It is common practice in pediatric oncology to use drugs in an off-label or non-FDA approved manner, which, in many cases, represents the standard of care. In clinical protocols for pediatric oncology, investigators determine how a drug should be used based on previous studies using the drug in adults, knowledge of the biology of the

disease and the mechanism of action of the drug, and past experience with dosing similar drugs in children. The protocols generally describe or reference any past experience with the drug in children and explicitly describe how the drug should be administered. Off-label use does not reflect inadequate scientific rationale for such use, but instead reflects the fact that the pharmaceutical sponsor of the drug has not conducted studies of the product in the pediatric population and/or has not submitted data to FDA for review. One reason data may not submitted is that there is a relatively small market potential for most pediatric cancer indications. Recognizing this hurdle, it is nevertheless critical to provide accurate and detailed information in the label as a guide to best possible use of these agents in the pediatric population. To obtain the best information for the label, it is imperative to perform well-conducted trials in children and submit the data to FDA.

IV. EXISTING PROGRAMS

A. Clinical Trials Networks

The most common route of access to an unapproved drug for children with cancer is through enrollment in a clinical trial.

Clinical trials for pediatric cancer patients can be broadly classified as those sponsored by NCI and those supported by non-government sources of funding. NCI sponsorship has provided support for a nationwide clinical trials program for children with cancer for more than four decades. The Cancer Treatment Evaluation Program (CTEP) is the center within NCI that facilitates the clinical development of new drugs, provides oversight of cooperative research groups, coordinates access to investigational drugs, and reviews the design of clinical research protocols. As part of the CTEP program, NCI sponsors the national cooperative cancer groups, including COG, the Pediatric Brain Tumor Consortium (PBTC, 10 institutions), the New Agents for Neuroblastoma Treatment Consortium (NANT, 12 institutions), and the COG Phase 1/Pilot Consortium. The COG Phase 1 consortium, a 22-center subset of COG, tests new agents for optimal dose and for toxicity so that promising agents can be prioritized for Phase 2 and Phase 3 trials. NCI also conducts clinical research in the Pediatric Oncology Branch, its intramural program. Approximately 4,000 children enroll annually in NCI sponsored clinical trials. Approximately 500 of these children enroll in trials evaluating one or more investigational agents. The following table summarizes accrual to clinical trials involving investigational agents sponsored by CTEP/NCI during 2002.

Table 1. NCI-sponsored pediatric trials using investigational agents 2002[5]

	Phase 1	Phase 2	Phase 3
Number of trials	28	15	7
Number of agents	24	11	7
Number of patients accrued	193	152	166
Lead organizations and numbers of trials	COG 3 COG Phase 1 7 NANT 3 PBTC 7 Pediatric Branch 7 Not stated 1	COG 12 Pediatric Branch 2 PBTC 1	COG 5 CALGB[1] 1 Pediatric Branch 1

[1] Cancer and Leukemia Group B, an NCI-sponsored cooperative research group that performs predominantly adult studies.

NCI also funds pediatric trials through Program Project grants and through conventional NCI investigator-initiated research. In addition to NCI-funded programs, pediatric oncology research programs at pediatric cancer centers are also supported by institutional, private, and commercial sources of funding. These programs perform predominantly Phase 1 and 2 studies, which explore the potential of new therapies. Pharmaceutical manufacturers sometimes conduct independent clinical trials, but because of the unique nature of pediatric cancer and its relatively small numbers of patients, these trials are generally performed within the clinical trials networks.

Approximately 90 percent of children with cancer are treated at member institutions of COG, and about 50 percent of children with cancer participate in clinical trials, with the proportion varying by age and by diagnosis. Because of this high rate of clinical trial participation, access to investigational agents may be improved by continued collaboration with the pharmaceutical industry to provide additional new drugs for studies in children and to provide them sooner. FDA and NCI continue to work together to ensure that appropriate pediatric protocols are written, reviewed, and opened to accrual promptly.

B. Access Outside of Clinical Trials

It is not always possible for all patients who want access to investigational drugs to enroll in clinical trials. Patients may not meet eligibility criteria or may be geographically isolated from a study site. It may be difficult to find an ongoing trial for a particular type

[5] A full list of these clinical trials is available at http://ctep.cancer.gov . Choose the Resources link, then the Childhood Cancer Resources link, and select the document titled *Access to Investigational Agents for Children with Cancer through Clinical Trials.*

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and stage of cancer. In these situations, FDA and NCI believe that it is appropriate to help make certain promising, but as yet unproven, products available outside of a clinical trial (non-protocol) to patients with cancer as well as other serious and life-threatening illnesses. Non-protocol investigational therapy should be offered in a way that does not pose an unreasonable risk to the patient or an unreasonable risk of losing valuable information about the effect of the drug. For these reasons, although treatment is focused on the individual patient, a study plan (protocol) may be written to ensure that the treatment is administered appropriately and that patients are monitored for toxicity. The programs available through both agencies are discussed below. It is important to note that a pharmaceutical manufacturer must first agree to provide the requested product for a non-protocol investigational therapy to begin. NCI and FDA cannot mandate that the requested products be supplied to these programs; the agencies can only review and approve proposals to use them.

1. FDA Programs for Non-protocol Access

FDA programs that permit non-protocol access to investigational agents for patients with serious or life-threatening disease include the single patient IND, the emergency IND, and the Treatment IND (sometimes informally referred to as an expanded access protocol). The lay public frequently refers to these programs as *compassionate use*, although the term *compassionate use* does not appear in FDA regulations. Single patient or emergency INDs refer to a treatment program for a single individual. Treatment IND refers to a single study plan used to treat multiple patients.

a) Single Patient IND Submissions

Single-patient IND submissions can represent entirely new uses for a drug or exceptions to an ongoing clinical trial protocol for a patient who does not meet protocol entry criteria. Single patient IND requests can be submitted as amendments to an existing IND or as an entirely new IND. They can be submitted by a drug manufacturer (usually amending an existing IND) or by an individual physician, following usual procedures for IND filing, including IRB review and informed consent. If the need for treatment is urgent and does not allow time for submission of an IND, an emergency IND can be obtained allowing FDA to authorize shipment of a drug for the specified use before the IND is submitted (21 CFR 312.36). The IND should then be submitted as soon as possible after receiving authorization. As with all INDs, both mechanisms require adverse event reporting and an annual summary to be submitted to FDA.

b) Treatment IND

Treatment IND study plans “facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and … obtain additional data on the drug’s safety and

effectiveness" (21 CFR 312.34). Certain criteria must be met for a drug to be considered for approval in a Treatment IND,[6] including:

- The patients' disease must be serious or life-threatening.
- No comparable or satisfactory treatment is available to the target population of patients.
- The drug is in clinical trials (generally Phase 3 and not ordinarily prior to Phase 2).
- The sponsor of the clinical trials is actively pursuing marketing of the drug.

FDA may refuse the request if:

- For a serious disease, sufficient evidence of safety and potential efficacy is not provided to support use of the drug to treat it.
- For a life-threatening disease, available scientific evidence does not provide a reasonable basis for concluding that the drug may be effective and would not expose patients to serious additional risk of illness or injury.

The same safeguards and reporting requirements that apply to any IND study apply to a Treatment IND, including IRB approval. The study plan must contain a rationale for the use of the investigational drug, as well as a list of what available regimens should be tried prior to its use, or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

c) Summary Data

FDA reviewed 557 single-patient IND submissions to the Center for Drug Evaluation and Research (CDER) and 135 emergency IND submissions in calendar year 2002, a total of 692 requests. The Center for Biologics Evaluation and Research (CBER) reviewed 94 single-patient INDs/protocol exceptions and 47 emergency INDs, a total of 141 requests. A summary of the findings is provided in Table 2.

[6] See 21 CFR 312.34

Table 2. FDA Single-Patient Use in Calendar Year 2002

Type of Request	Total Number of Requests Received	Number of Requests Identified as Pediatric	Number of Pediatric Requests Identified as Pediatric Oncology
CDER Single Patient IND	557	Not Available*	Not available*
CDER Emergency IND	135	Not available*	Not available*
CBER Single Patient IND/Protocol Exceptions	94	13 (14%)	6
CBER Emergency IND	47	5 (11%)	1

*Currently, CDER does not tabulate information on age electronically

Because Treatment INDs do not have separate designations in FDA tracking system, information on these treatment plans is not available.

Most of the single-patient IND requests submitted to FDA are approved.

2. NCI Programs for Non-protocol Access

At NCI, Special Exception and Group C protocols provide access to investigational agents for those patients unable to participate in a clinical trial.

a) Special Exception

The Special Exception is comparable to the single patient IND, but investigators may obtain investigational agents directly from NCI using NCI's Special Exception mechanism instead of filing a new IND with FDA. NCI does not grant these requests for drugs in Phase 1 development, because NCI requires some demonstration of efficacy before permitting individual treatment. The written policy for this program requires objective evidence that the investigational agent is active in the disease for which the request is being made.
Anecdotal reports or reports that show low response rates or responses of brief duration are not sufficient to justify approval of the request. Patients must be ineligible for ongoing research protocols and must have received standard therapies.

b) Group C

Group C designation is an expanded access program similar to a Treatment IND that allows broadened access to investigational agents with reproducible activity in one or more specific tumor types. An agent must alter or be likely to alter the pattern of treatment of the disease, and properly trained physicians without specialized supportive care facilities must be able to administer the agent safely. For an agent that meets this definition, CTEP may submit a formal application to FDA to authorize distribution of the agent (Group C distribution) by NCI for the specific indication described in the application. This application is not a marketing application, and FDA approval of a Group C protocol does not replace an FDA conclusion that the drug is safe and effective. The study plan must contain the indication, dosage, precautions, warnings, known adverse events of the product, and an informed consent form. Approval of the Group C protocol carries the obligation of the usual safety reporting requirements. This mechanism is used only with agents for which activity is sufficiently established and for which a New Drug Application (NDA) or Biological Licensing Application (BLA) approval is considered likely in the relatively near future.

c) Summary Data

A summary of approvals and denials under NCI's Special Exception Program for the calendar year 2002 is provided in Table 3. Information is not available regarding how many of the denials, if any, were for pediatric patients.

Table 3. NCI Special Exception Data for Calendar Year 2002

Total Requests	1277	Percent of Total
Approvals[1]	541	42%
Referrals to existing protocols	505	39%
Denials	231	18%

[1]Of the total approved requests, 79 (15% of *approvals*) were for pediatric access.

The reasons for the small numbers of requests from pediatric cancer patients for non-protocol access are multiple and likely include: (1)
availability of some investigational agents for pediatric patients through Phase 1 and Phase 2 protocol mechanisms,
(2) ability to obtain access to commercially available agents for pediatric use, (3) strong support in the pediatric oncology community for the clinical trial mechanism, and (4) inability to extrapolate preliminary data on safety and effectiveness of investigational agents from adult cancers to pediatric cancers.

The Group C mechanism is used less commonly, superceded by other NCI and FDA programs. At present, there is one active Group C protocol at NCI.

3. Non-protocol Access through Pharmaceutical Companies

FDA and NCI do not have data on how many requests were made directly to pharmaceutical companies for access to unapproved or investigational agents or how many were granted.

4. Summary and Conclusions

Based on data from NCI and FDA for calendar year 2002, the number of children who received investigational drugs off protocol represent less than 0.5 percent of the approximately 20,000 children with cancer who are treated in any given year. The 2002 data are consistent with information from previous calendar years. These programs provide a secondary mechanism for investigational drug access for patients who cannot participate in a study.

C. Public Access to Information about Investigational Products

A critical part of ensuring that patients have adequate access to investigational agents is to make public information about investigational products readily available. Some sources of information about clinical trials include listings of clinical trials on government-sponsored Internet sites, such as http://www.clinicaltrials.gov, maintained by the National Library of Medicine (NLM). Non-government sponsored Internet sites also provide information on clinical trials.

Launched in February 2000, the Clinical Trials Data Bank[7] was established by the NLM through a cooperative effort between NIH and FDA, as directed in FDAMA, section 113, amending the United States Code (42 U.S.C. 282)). FDAMA mandated the establishment of this public resource for information about drug studies, conducted under FDA's IND regulations (21 CFR 312), for serious or life-threatening diseases. The Clinical Trials Data Bank is available to the public through the Internet and currently has information concerning approximately 7,000 clinical studies sponsored by NIH, other Federal agencies, and the pharmaceutical industry in over 77,000 locations worldwide. More than 2,000 of the trials listed are investigating cancer-related indications, and approximately 100 of the trials are investigating agents for pediatric cancer. Studies listed in the database are conducted primarily in the United States and Canada, but the database includes locations in approximately 80 countries. ClinicalTrials.gov receives more than 3 million page views each month and hosts about 9,000 visitors daily.

[7] http://www.clinicaltrials.gov

Section 15 C(2) of BPCA, amending the Public Health Services Act at section 402 (j)(3)(A)[8], requires that, in addition to providing information about clinical trials, the Clinical Trials Data Bank should contain information about possibilities for treatment use of investigational drugs. The required information should include whether "the manufacturer or sponsor of the investigation of a new drug will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded protocol use of the new drug, particularly in children" and how to make a request. The Clinical Trials Data Bank has been updated to include a new field to comply with this requirement. Additional revisions and guidance will be provided when FDA Guidance for industry on the *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions* is updated.

Although the Clinical Trials Data Bank is a valuable resource for information, it is not a comprehensive list of all clinical trials underway. Regulations require that studies performed in patients with serious and life-threatening diseases be listed. Because listing studies that do not meet the threshold is optional, patients and their physicians may have difficulty identifying all relevant trials. It is important to note that FDA is prohibited from divulging proprietary information, such as whether a sponsor has filed an IND or what the status of an IND is. Because of that, FDA is not permitted to refer callers to open clinical trials or non-protocol treatment sources for a promising new drug. Interested individuals must obtain this information from other sources.

NCI has additional information resources available through various specialized programs. The Treatment Referral Center program, for example, provides information to community oncologists, emphasizing referrals to cooperative group studies or cancer centers. This program uses the Clinical Trials Data Bank and the PDQ® (Physician Data Query),[9] CTEP information systems databases, data submitted by NCI-designated Comprehensive Cancer Centers, and consultation with CTEP physicians to maintain a referral list of active treatment programs. This system allows patients to (1) be referred to a Phase 2 or Phase 3 cooperative group study or to a participating cancer center for evaluation for an investigational protocol, (2) receive information about standard treatment options, and (3) inquire about potential eligibility for Group C or Special Exception agents.

Additional sources of information about clinical trials include physicians and other health professionals who specialize in the care of cancer patients, patient advocacy groups, and NCI's Cancer Information Service.[10] Individuals can call the Cancer Information Service to obtain information about cancer, its treatment, and investigational programs.

[8] 42 U.S.C. 282
[9] http://www.cancer.gov/search/clinical_trials/
[10] 1-800-4CANCER (1-800-422-6237)

D. Legislation

Increased access to information about clinical trials and the high rate of participation of pediatric cancer patients contribute significantly to the effort to find new and better drugs to treat children with cancer. These trials require the cooperation of the pharmaceutical industry to make new drugs available for pediatric testing. However, products frequently are not made available because of the small pediatric market or because of concerns about safety in children. FDA is committed to the development of effective and safe therapies for childhood malignancies. During the past decade, FDA has worked to develop and support regulatory initiatives and legislation designed to stimulate pediatric therapeutic development among pharmaceutical manufacturers.

1. The 1998 Pediatric Rule

The 1998 Pediatric Rule required that all NDAs or BLAs contain data adequate to assess a drug's safety and effectiveness for the requested adult indication in all relevant pediatric subpopulations, including information sufficient to support dosing and administration in children for those indications. The Pediatric Rule required all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless the requirement was waived or deferred (*Federal Register*, December 2, 1998*,* 63 FR 66632). Based on standard tumor classifications, the prevailing belief was that application of the Pediatric Rule to pediatric oncology would be limited because children and adults have different types of cancer, with relatively few types in common. However, in re-examining the linkages among cancer types using modern scientific criteria, the Pediatric Subcommittee of FDA's ODAC identified several tumor types to which the Rule could apply. Application of the Rule would provide valuable information for children with cancer and their treating physicians.

The Pediatric Rule was invalidated on October 17, 2002, by the Federal District Court for the District of Columbia, which stated that the agency did not have the authority to issue the rule. Congress is currently considering legislation to provide FDA with additional authorities to ensure that medicines intended for use in pediatric sub-populations are adequately studied.

2. Pediatric Exclusivity Program

The Pediatric Exclusivity program, previously part of FDAMA and now incorporated in BPCA, is a voluntary program that directs FDA to request pediatric studies from sponsors to address public health needs. Under this program, FDA issues a Written Request that describes (1) pediatric information that FDA considers important for the development of the product and (2) the types of studies that would produce this information. A sponsor may accept or decline the Written Request. If the Written Request is accepted, the sponsor conducts the requested studies and submits reports

to FDA for review. FDA determines whether the studies fairly respond to the Written Request. If the studies are responsive, then all of the sponsor's products that contain the same active moiety and have existing patent or exclusivity protection will qualify for an additional 6 months of exclusivity. Pediatric Exclusivity will be granted, whether or not the studies demonstrate efficacy or safety as long as the studies fairly respond to the terms of the Written Request.

In addition, the BPCA establishes other mechanisms for obtaining information on the safe and effective use of drugs in pediatric patients. First, the BPCA authorizes the NIH to fund studies of drugs that no longer have exclusivity or patent protection when pediatric information is needed. Second, for drugs that have patent or exclusivity protection, but for which the sponsor has declined to conduct the pediatric studies in response to a Written Request, the BPCA provides for referral of the drug to the Foundation for the National Institutes of Health to award a grant to conduct the requested pediatric studies, when funds are available. After receiving a referral from FDA, the Foundation will issue a proposal to award a grant for conducting the requested pediatric studies.

FDA developed a special program for pediatric oncology Written Requests and issued a guidance for industry, *Pediatric Oncology Studies In Response to a Written Request*, in June 2000.[11] FDA has issued Written Requests under this program to the manufacturers of about 30 cancer products. Approximately half of the Written Requests were issued for products under development. As of December 2002, four products to treat cancer have been granted exclusivity, and information on pediatric use has been added to their labeling.

V. RECENT INITIATIVES TO IMPROVE ACCESS

Successful means of improving access include clinical trial participation, readily accessible information about investigational trials, and legislation to encourage pediatric drug development. New measures to improve access further are discussed below.

A. New Programs to Identify Challenges to Pediatric Drug Development

1. July 2002 Workshop on Pediatric Oncology Drug Development

FDA and NCI co-sponsored a workshop in July 2002[12] (in partnership with the American Academy of Pediatrics, COG, and the Alliance for Childhood Cancer) to discuss drug development in pediatric oncology, including prioritization of promising new agents,

[11] Available at http://www.fda.gov/cder/guidance/
[12] Available at http://www.fda.gov/cder/cancer/presentations/WorkshopJuly2002.htm

clinical trial design, and access to new therapies. The purpose of the workshop was to identify issues that impede pediatric drug development and to frame these issues for consideration by the Pediatric Subcommittee of FDA's ODAC. Some highlights from the Workshop proceedings follow.

a) Numbers of New Agents for Children

Workshop participants first addressed why only a small number of new agents are developed for pediatric cancer patients compared to the number developed for adults. Although pediatric cancer poses a significant public health problem, the number of patients with specific cancer types and appropriate clinical trial eligibility characteristics is small. Each year, between 12,000 and 13,000 children are diagnosed and about 20,000 receive treatment for all types of pediatric malignancies combined. Some of the rare types of pediatric tumors will be found in perhaps a few dozen patients. In comparison, more than 1 million adult patients are diagnosed with cancer in the United States annually. Each year, more than 170,000 adults are diagnosed with lung cancer, more than 200,000 women are diagnosed with breast cancer, and more than 220,000 men are diagnosed with prostate cancer. Comparatively few pediatric patients are available to participate in clinical trials.

While the goal is to reduce the numbers even further, the relatively small number of children with cancer poses several challenges to studying new pediatric cancer treatments. First, children with cancer do not provide a large market for pharmaceutical companies. Investigator access to drugs appropriate for pediatric clinical trials, therefore, may be limited. Second, the small number of patients means that few drugs can be studied in a single cancer type. Phase 3 studies usually enroll only untreated patients and typically require from 3 to 7 years to complete. Third, Phase 3 trials are powered to show a difference between treatments. As survival for many types of pediatric cancer improves, more patients must enter a clinical trial in order to demonstrate effectiveness of new treatments statistically. FDA, NCI, and COG will face challenges in prioritizing individual drugs for study and reconciling these priorities with FDA's Written Requests for Pediatric Exclusivity. Industry representatives at the workshop noted that even with Orphan Products provisions, the small pediatric oncology patient population is still well below the threshold at which drug development yields a return on investment. Effective means of addressing these challenges include: (1) better methods for preclinical screening of new drugs in order to prioritize the most promising agents, (2) research into molecular disease mechanisms that might yield new therapeutic targets or surrogate endpoints that decrease sample size or study length, and (3) continued incentives for industry.

b) Delays in Initiation of Pediatric Trials

Workshop participants noted that clinical testing of new drugs in pediatric oncology lags behind adult testing. One presentation reported that Phase 1 pediatric studies were

initiated an average of more than 2 years after the adult Phase 1 studies were published. Delays in the initiation of pediatric studies occur for several reasons. When companies have a limited supply of a drug, enrollment is generally restricted to higher priority (for marketing) adult studies. Manufacturers may not develop an appropriate pediatric formulation until adult Phase 1 data are available, further slowing access to young children for drugs that require oral formulations. There is also frequently a perceived ethical need to demonstrate safety and activity in adult patients prior to initiating pediatric studies. A related concern in the pharmaceutical industry is the perceived risk of legal liability and regulatory delay of approval from any toxicity in children that may occur during the study of any investigational agent.[13] Finally, for financial reasons, drugs that look promising in early phase trials in children may not be developed if there is little activity in adults.

A commitment to pediatric drug development from pharmaceutical manufacturers is critical to expanding access and providing new treatments for pediatric cancer. In order to speed drug development in children, the workshop panel recommended encouraging sponsors to begin pediatric Phase 1 studies as soon as adult Phase 1 studies are complete. The panel agreed that adult studies should be completed first so that adult dosing and toxicity are characterized before testing in children. These data can be used to select an appropriate pediatric starting dose without subjecting many children to doses that are too low for a potential therapeutic effect or too high, causing excessive toxicity. The data can also be used to avoid pediatric testing of drugs that are inappropriately toxic.

c) Need for New Pediatric Clinical Trial Designs

During the workshop, the participants concluded that new clinical trial designs should be considered in order to evaluate new therapies efficiently. Surrogate markers (measurements that substitute for clinical endpoints that are difficult to study) could be considered as an early means of identifying efficacy, but the use of surrogates requires validation of these markers and correlation with clinical benefit. The panel discussed the potential role of COG Phase 1 correlative studies in acquiring this information.

d) Pediatric Access to New Therapeutic Agents

Workshop participants agreed that the optimal means of providing access to investigational agents is through enrollment of patients in clinical trials. Treatment with investigational agents outside of a clinical trial setting could result in the loss of potentially credible information and could expose children to unknown risks. In addition, diverting patients (i.e., potential study participants) to off-protocol access could compromise clinical studies. The panel emphasized that information derived from

[13] To examine this point further, FDA conducted an internal review of all cancer-related IND applications that were placed on clinical hold and was unable to identify a single instance of a cancer drug development program encountering a regulatory delay due to a pediatric toxicity.

clinical trials, not from individual patient experiences, has driven the improvements in survival rates for children with cancer over the past decades. Pediatric oncology treatment takes place in clinical trials probably to a greater extent than any other medical specialty in the United States. Rapid development of protocols would decrease pressure to obtain investigational drugs on an individual basis and would allow more patients access to promising therapies. With better understanding of cancer biology and the development of new classes of potential therapies, it is incumbent upon investigators to anticipate the need for new studies and to activate protocols quickly. Further research into cancer biology and continued training of academic pediatric oncologists is important.

Workshop participants also discussed off-protocol or individual access to investigational drugs. Though protocol enrollment should always be considered first, it may not always be feasible. The panel discussed criteria for determining when individual access might be appropriate. Because parents request access for their children — a vulnerable population requiring protection — the participants recommended that an open and informed discussion about the best interests of the child should precede any exposure to investigational drugs.

2. Pediatric Oncology Subcommittee of ODAC

The Pediatric Oncology Subcommittee of FDA's ODAC was established in September 2000 and has convened six meetings to date.[14] Pediatric specialists from NCI participate as panel members. The Workshop discussed in the previous section prioritized issues in pediatric drug development for consideration by the subcommittee.

The first four meetings (9/12/00, 4/24/01, 6/28/01, 11/28/01) discussed the application of the Pediatric Rule to pediatric oncology. At the time, the Rule was in effect and required sponsors of NDAs and BLAs under review for an adult indication that also exists in children to submit pediatric studies as part of the application if the product represented a therapeutic advance or would have widespread use in children. The subcommittee members discussed the basis for diagnosing and classifying tumors and made recommendations regarding which tumors were substantially similar in adults and children. The subcommittee concluded that there was a sufficient basis to warrant coordinated adult and pediatric development for (1) acute leukemias, (2) anaplastic, diffuse large cell, Burkitt's and lymphoblastic lymphomas, (3) brain tumors, and (4) solid tumors. The subcommittee further recommended that, for pediatric tumors similar to adult tumors, pediatric dosing and safety studies with a *proof of concept* study (demonstrating that the pediatric dose would produce tumor responses similar to those seen in adult studies) would be adequate to extend efficacy findings to the pediatric population. Clinical outcome data would not be necessary.

The fifth meeting (10/17/02) discussed the timing of the initiation of pediatric oncology studies in a drug development program. The meeting resulted in a consensus

[14] Advisory Committee meeting information is available at http://www.fda.gov/cder/

statement on the initiation of Phase 1 trials of investigational drugs in children with cancer when no other therapeutic options exist. The following statements represent the subcommittee consensus:

(1) Pediatric oncology drug development should generally be coordinated with oncology drug development for adults as part of an overall drug development plan.

(2) Evidence required prior to initiating clinical studies in pediatric cancer patients includes data to support the potential for biological activity against a pediatric tumor (preclinical data could suffice), some expectation of potential benefit, a reasonable expectation of safety, and sufficient information to choose an appropriate starting dose.

(3) Case-by-case determinations of when to initiate pediatric oncology studies can be made on the basis of the type of agent, the mechanism of action, what is known about the safety profile, and the potential indication.

(4) If a scientific rationale for use of a product in a population of pediatric cancer patients with no available anti-cancer therapy exists, then pediatric oncology clinical studies should be initiated immediately following adult Phase 1 studies.

(5) As preclinical models are validated for activity, pharmacology, and safety, the necessity of adult studies prior to pediatric studies may diminish, and pediatric patients may be the first patients to receive a new agent. This is particularly relevant to agents directed against childhood cancer therapeutic targets that are not applicable to any adult cancers.

At the sixth meeting of the Pediatric Oncology Subcommittee (3/4/03), subcommittee members discussed case studies of pediatric supplements for oncology products submitted in response to a Written Request. The subcommittee was asked to recommend necessary and appropriate labeling information for drugs studied in children. Subcommittee members discussed several scenarios, including drugs with indications that exist in children and adults, drugs with an adult indication that does not exist in children, and cases where a drug trial in children did not demonstrate efficacy.

These recommendations are intended to facilitate a more timely and rational introduction of new agents into the pediatric population, including mechanisms to permit extrapolation from adult efficacy data to a relevant pediatric population in a consistent and scientifically valid manner.

3. Role of Pharmaceutical Industry

NCI, COG, and FDA have initiated formal exchanges with the pharmaceutical industry about the development of new agents for pediatric oncology. In 2002, the pharmaceutical industry formed an organization of pediatric oncologists, which has had

representatives at meetings of the Pediatric Oncology Subcommittee of FDA's ODAC and COG. This dialogue — geared toward cooperation and information sharing — is critical to forming a mutual collaboration to make new drugs available to children with cancer.

4. Summary

Discussion at the July 2002 Workshop on Pediatric Oncology Drug Development identified areas in pediatric drug development that could be improved to facilitate access to new agents. The Pediatric Oncology Subcommittee meetings were designed to discuss and provide advice on these issues. Future meetings are scheduled. Because of these HHS collaborations, new liaisons have been formed with the pharmaceutical industry. Pediatric labeling changes have been approved for four drugs, and FDA continues to issue new Written Requests.

B. New Programs Designed to Encourage Drug Development

The discussions at the Workshop and within the pediatric subcommittee of ODAC included recommendations for better preclinical estimates of efficacy and continued incentives for the pharmaceutical industry. This section of the report describes new programs developed at NCI to help address these recommendations.

1. Preclinical Screening Program

Because there are few pediatric patients with each specific tumor type, the number of patients eligible for Phase 2 and Phase 3 trials in a selected disease is small. For example, due to a sample size limitation, it takes from 4 to 5 years to conduct a Phase 3 study in a disease such as neuroblastoma. The potential number of therapies and combination treatments for children is large, but because patient population size for clinical testing is small, it would be helpful to identify preclinically the agents most likely to be active. Because of the scarcity of patient resources, the best potential agents should be selected and prioritized for study.

In order to help accomplish this goal, NCI recently received approval from its Board of Scientific Advisors to develop a Pediatric Preclinical Testing Program. The goal of the program is to identify preclinical models that can be used to select new agents that demonstrate clinical activity against specific types of childhood cancer. At present, there are no pediatric tumors occurring solely in children represented in the standard NCI panel of cell types that are used to screen potential anti-cancer compounds. This program would test the ability of new drugs to kill pediatric cancer cell lines grown in culture or in animals, for activity resulting in slowed cell growth rates, prolonged animal survival rates, or delayed disease progression. If successful, the program could expedite discovery of more effective treatments for children with cancer.

This program will also include tests of pediatric tumor tissue and pediatric tumor cell lines for gene and protein expression. The results will facilitate preclinical testing of new, promising, targeted therapies and treatments designed to inhibit a specific gene or protein important in the development of a particular type of pediatric cancer. Several new treatments that target the same gene or protein can be tested preclinically in a tissue known to express the target and may determine which treatment has the best chance for success. Finally, this program could identify drugs potentially useful in pediatric but not adult malignancies that otherwise might be missed if investigators relied only on adult clinical trial data.

2. NCI Small Business and Investigator Grants

Over the past few years, NCI has initiated several programs aimed at stimulating new drug development for cancer patients. Because there is a limited pool of academic researchers investigating pediatric cancers, NCI directed its efforts toward the biotechnology industry. The programs developed include Small Business Innovation Research (SBIR) grants, Small Business Technology Transfer grants, the Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses program, and the Rapid Access to Intervention Development grant program. While not specifically directed toward pediatric oncology, any of the programs can be used to develop candidate drugs. A recent NCI initiative solicited applications from the small business community for research projects to identify new agents that specifically target childhood cancers. The SBIR program recently issued a call for contract proposals (PHS 2003-1) titled, **"**Development of Novel Agents Directed Against Childhood Cancer Molecular Targets."

FDA provides direct grants to pharmaceutical companies and to investigators developing products for orphan diseases through the Orphan Product Development program for clinical studies. It also provides an incentive through BPCA that allows an additional 6-month extension of marketing exclusivity.

VI. FUTURE APPROACHES

Pediatric patients have access to new oncology drugs primarily through participation in clinical trials, a process through which NCI, FDA, clinical investigators, and pharmaceutical sponsors throughout the country work closely together. The application of evidence-based medicine resulting from the clinical trials process is a critical factor in the notable increase in survival rates of pediatric cancer patients. Despite these successes, challenges remain. NCI and FDA, working together in the Department of Health and Human Services, have identified the following approaches to improving access:

- Reliable prioritization of the best potential agents for clinical testing in children with different types of cancer through systematic evaluation of new agents in childhood cancer preclinical models. NCI's Pediatric Preclinical Testing Program will contribute to this aim but will need the support of pharmaceutical sponsors to meet its objectives. New preclinical models of childhood cancers may also be needed to better identify new agents that should be tested in children.

- Further research into the biological mechanisms of pediatric tumors. This type of research might improve the development of new therapies by identifying biologic mechanisms common to adult and pediatric tumors, encouraging earlier testing in children or use in a pediatric tumor not anticipated by conventional tumor classification.

- Continued identification of products meriting a Written Request from FDA to a pharmaceutical sponsor to conduct studies and potentially qualify the product for Pediatric Exclusivity.

- Continued collaboration with the pharmaceutical industry to make new agents available for evaluation in children at an appropriate time in a drug's development.

- Ongoing training of qualified pediatric researchers and physicians to maintain the current high level of care.

- Continued support of pediatric clinical research programs to obtain safety and efficacy information through appropriately conducted clinical trials.

By working together as a department, NCI and FDA will pool their resources to improve outcomes for children with cancer.