Regulatory Approvals of Pediatric Oncology Drugs: Previous Experience and New Initiatives

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Purpose: **To review the Food and Drug Administration (FDA) experience with approvals of new drugs for pediatric oncology and to discuss new regulatory initiatives directed at pediatric oncology.**

Methods: **A retrospective review of FDA archival documents and the published literature.**

Results: **More than 100 drugs have been approved by the Division of Oncology Drug Products of the FDA for the treatment of malignancies. Only 15 have pediatric use information in their labeling, which is less than 50% of the drugs commonly used in the treatment of pediatric malignancies. In the past 20 years, there have been six submissions to the FDA for pediatric oncology indications. To illustrate principles of the approval process, each submission is discussed.**

Conclusion: **Potential reasons for a lack of New Drug Application submissions for pediatric oncology include the small pediatric oncology market compared with the adult oncology market and perceived barriers to performing studies in children. Reasons for failure to approve pediatric indications include small numbers of patients, lack of appropriate controls, and failure to demonstrate patient benefit. Approval criteria include the use of controlled trials, prospective data collection, and disease-appropriate end points. Regulatory initiatives to promote pediatric therapeutic development and product labeling are discussed.**

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CHILDHOOD CANCERS are rare, accounting for less than 1% of the one million patients diagnosed with cancer in the United States each year.[1] There are between 12,000 and 15,000 pediatric patients per year for all pediatric cancer combined, compared with the more than 170,000 adult patients who are diagnosed with lung cancer, 175,000 adult patients who are diagnosed with breast cancer, and 179,000 adult patients who are diagnosed with prostate cancer annually. Nevertheless, cancer remains the most common fatal disease of childhood.

More than 100 drugs are approved by the Food and Drug Administration (FDA) for the treatment of malignancies. Bleyer et al[2] noted that about 30 approved drugs are currently used in pediatric oncology. Fifteen of these drugs, listed in Table 1, have been labeled for use in children. The inclusion criteria for this listing are 1) a specific reference to pediatric patients or a pediatric malignancy in the "Indications and Usage" section, 2) approval in a disease setting exclusive to pediatrics (eg, neuroblastoma or Wilms tumor), and 3) specific information regarding pediatric dosing in the "Dosage and Administration" section. The first two criteria provide the most unequivocal support for the use of a drug in pediatric oncology. The 15 drugs that meet these criteria are L-asparaginase, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, doxorubicin, lomustine, mercaptopurine, methotrexate, procarbazine, teniposide, thioguanine, tretinoin, vinblastine, and vincristine.

The FDA approved these drugs predominantly in the 1950s and 1960s. Since 1980, only one new molecular entity, teniposide (Vumon, formerly known as VM-26; Bristol-Myers Squibb, Princeton, NJ), has been labeled for use in a pediatric malignancy (refractory leukemia) compared with more than 50 new molecular entities approved for adult oncology indications. Possible reasons for the disparity between adult and pediatric FDA approvals include the relative rarity of childhood malignancies, the histopathologic and biologic differences between many adult and pediatric tumors, and the limited number of pediatric patients eligible for pharmaceutical trials.

Table 2 lists 26 commercially available oncology medications that are currently prescribed in pediatric oncology, the conditions for which they are prescribed, and whether a pediatric indication or pediatric dosing is in the product label. As an example, none of the three components of the "ICE" (ifosfamide, carboplatin, and etoposide) regimen, which is widely used for relapsed pediatric malignancies, has ever been approved for pediatric use. In addition, the combination of ifosfamide and etoposide has been incorporated into treatment for all patients in a recent cooperative group Ewing's sarcoma study (Grier HE, personal communication, 1998). Similarly, cisplatin, originally approved in 1978 and at present prescribed in initial therapy for neuroblastoma,[3,4] hepatoblastoma,[5] and germ cell tumors,[6] lacks specific pediatric labeling.

The FDA has the responsibility of approving marketing claims about the use of a drug. To be considered for marketing approval, sponsors must submit to the FDA a New Drug Application (NDA). An NDA must contain detailed information regarding the product's chemistry and manufacturing, preclinical toxicology, pharmacology, and clinical investigations. In addition to intensive review by FDA scientists, NDAs are often

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Table 1. Fifteen Oncology Drugs Approved for Pediatric Use With Pediatric Dosing Information in the Label

Drug	Indication
L-Asparaginase	Leukemias
Cyclophosphamide	Leukemias, lymphomas, neuroblastoma, retinoblastoma
Cytarabine	Acute nonlymphocytic leukemia in adults and children
Dactinomycin	Wilm's tumor, rhabdomyosarcoma, choriocarcinoma, testicular carcinoma, Ewing's sarcoma, sarcoma botyroides
Daunorubicin	Acute lymphocytic leukemia in adults and children
Doxorubicin	Wilm's tumor, neuroblastoma, soft tissue sarcomas, Hodgkin's disease, other malignant lymphomas, acute lymphocytic leukemia, acute myelogenous leukemia
Lomustine	Brain tumors, Hodgkin's lymphoma
Mercaptopurine	Acute lymphocytic leukemia in adults and children
Methotrexate	Acute lymphocytic leukemia, meningeal leukemia, osteosarcoma, non-Hodgkin's lymphomas
Procarbazine	Hodgkin's lymphoma
Thioguanine	Acute Non-lymphocytic leukemia
Teniposide	Refractory childhood acute lymphocytic leukemia
Tretinoin	Acute promyelocytic leukemia
Vinblastine	Histiocytoses, testicular germ cell carcinomas, Hodgkin's lymphoma
Vincristine	Acute leukemias, lymphomas, Wilm's tumor, rhabdomyosarcoma, neuroblastoma

reviewed and discussed by the Oncologic Drug Advisory Committee (ODAC), an external panel comprising oncologists, a statistician, a patient representative, and a consumer representative. In an open public forum, the sponsor and the FDA present findings to the ODAC, which makes a recommendation to the FDA regarding the approvability of the marketing claim for a drug. On the basis of the internal recommendations of FDA review staff and the ODAC, the FDA subsequently determines the approvability of the marketing claim and recommendations for the drug's use to be included in the package insert.

The approved claim is summarized in the product label (package insert) and constitutes the marketing license. All advertising and use claims are based on the label text. Once an NDA is approved, a pharmaceutical sponsor may subsequently submit a supplemental application (sNDA) to expand or modify the drug's use, including additional indications, modifications of dosage forms or dosing schedules, and different target populations.

As summarized in Table 3, the Center for Drug Evaluation and Research (CDER) of the FDA has reviewed six pediatric submissions involving five drugs during the period from 1979 to June 2002. Teniposide was approved for the therapy of relapsed acute lymphocytic leukemia (ALL). Daunorubicin (Cerubidine; Wyeth-Ayerst, Philadelphia, PA) was initially not approved for pediatric ALL and acute myelogenous leukemia (AML) but was subsequently approved for adult AML in 1979. An sNDA for its use in pediatric ALL was approved in 1983. An sNDA proposing the addition of osteosarcoma as a labeled indication for methotrexate was approved in 1988. Two asparaginase preparations, native *Escherichia coli* and polyethylene glycol–formulated *E. coli*, are considered biologic agents by the FDA and were reviewed and approved for use in pediatric ALL by the Center for Biologics Evaluation and Research (CBER) in 1978 and 1993, respectively.

Table 2. Pediatric Uses and Label Status of 30 Approved Oncology Drugs

Drug	Pediatric Use	Approved Indication?	Approved Dosing?
Asparaginase	Lymphomas		
	Acute lymphocytic leukemia	Yes	Yes
Bleomycin	Germ cell tumors		
	Lymphomas		
	Testicular		
Busulfan	Conditioning regimen		Yes
Carboplatin	Brain tumors		
	Germ cell tumors		
	Neuroblastoma		
Carmustine	Brain tumors		
	Lymphomas		
Cisplatin	Germ cell tumors		
	Neuroblastoma		
	Osteosarcoma		
	Testicular tumors	Yes	
	Brain tumors		
Corticosteroids			
Dexamethasone	Brain tumors		
	Leukemias	Yes	
	Lymphomas		
Prednisolone	Acute lymphocytic leukemia	Yes	
	Lymphomas		
Prednisone	Lymphomas		
	Histocytoses		
	Leukemias		
Cyclophosphamide	Sarcomas		
	Leukemias	Yes	Yes
	Lymphomas	Yes	Yes
	Neuroblastoma	Yes	Yes
	Retinoblastoma	Yes	Yes
Cytarabine	Leukemias	Yes	Yes
	Lymphomas		
Intrathecal	Meningeal leukemia	Yes	Yes
Dacarbazine	Hodgkin's lymphoma		
	Neuroblastoma		
	Sarcomas		
Dactinomycin	Neuroblastoma		
	Sarcomas	Yes	Yes
	Wilms tumor	Yes	Yes
	Testicular carcinoma	Yes	Yes
Daunorubicin	Acute lymphocytic leukemia	Yes	Yes
	Acute nonlymphocytic leukemia		
Doxorubicin	Acute lymphocytic leukemia	Yes	Yes
	Acute nonlymphocytic leukemia	Yes	Yes
	Lymphomas	Yes	Yes
	Sarcomas	Yes	Yes
	Wilms tumor	Yes	Yes
	Neuroblastoma	Yes	Yes
	Hodgkin's lymphoma	Yes	Yes
Etoposide, VP-16	Acute lymphocytic leukemia		
	Acute nonlymphocytic leukemia		
	Neuroblastoma		
	Sarcomas		
	Testicular tumors	Yes	
	Lymphomas		
	Brain tumors		
Fluorouracil	Hepatic tumors		
Ifosfamide	Germ cell tumors	Yes	
	Sarcomas		
	Lymphomas		
Isotretinoin	Neuroblastoma		
Lomustine	Brain tumors	Yes	Yes
	Hodgkin's lymphoma	Yes	Yes

Table 2. Pediatric Uses and Label Status of 30 Approved Oncology Drugs (Continued)

Drug	Pediatric Use	Approved Indication?	Approved Dosing?
Mechlorethamine	Brain tumors		
	Hodgkin's lymphoma	Yes	
Melphalan	Leukemias		
	Sarcoma		
	Neuroblastoma		
	Rhabdomyosarcoma		
Mercaptopurine	Acute lymphocytic leukemia	Yes	Yes
	Chronic myelogenous leukemia		
Methotrexate	Acute lymphocytic leukemia	Yes	Yes
	Non-Hodgkin's lymphomas	Yes	Yes
	Osteosarcoma	Yes	Yes
	Histiocytoses		
Intrathecal	Meningeal leukemia	Yes	Yes
Procarbazine	Brain tumors		
	Hodgkin's lymphoma	Yes	Yes
Teniposide, VM-26	Neuroblastoma		
	Sarcomas		
	Lymphomas		
	Brain tumors		
	Acute nonlymphocytic leukemia		
	Refractory acute lymphocytic leukemia	Yes	Yes
	Testicular tumors		
Thioguanine	Acute nonlymphocytic leukemia	Yes	Yes
	Acute lymphocytic leukemia		
Topotecan	Neuroblastoma		
Tretinoin	Acute promyelocytic leukemia	Yes	Yes
Vinblastine	Histiocytoses	Yes	Yes
	Hodgkin's lymphoma	Yes	Yes
	Testicular tumors	Yes	Yes
Vincristine	Acute leukemias	Yes	Yes
	Lymphomas	Yes	Yes
	Rhabdomyosarcoma	Yes	Yes
	Wilms tumor	Yes	Yes
	Non-rhabdo sarcomas		
	Neuroblastoma	Yes	Yes

During this 23-year period, the National Cancer Institute and pediatric cooperative groups were actively engaged in numerous clinical studies. A careful review of the pediatric oncology drug submissions to CDER over the past 20 years was conducted to examine the apparent discrepancy between approvals and research activity.

Vindesine for Acute Lymphocytic Leukemia

The sponsor, Eli Lilly (Indianapolis, IN), originally submitted this NDA for the use of vindesine in vincristine-refractory ALL patients in 1980. Although 71 patients treated in seven different phase I or II protocols at 18 different institutions were presented, only 16 patients were confirmed as being vincristine refractory. The overall response rate in this subset was 38%, with a median duration of response of 2.1 weeks.

The FDA review did not recommend approval of this submission. The decision was based on the short response duration and the difficulty in applying the findings to clinical practice because vindesine was unlikely to be used as a single agent for induction. The ODAC concurred and voted unanimously (7 to 0) against approval.

Table 3. FDA Actions on NDA Submissions for Pediatric Indications or Supplements From 1980 to 2001

Drug	Year	Indication	FDA Action
Vindesine	1980	ALL	Not approved
Teniposide	1981	Neuroblastoma	Not approved
Daunorubicin	1983	ALL	Approved as supplement
5-Azacytidine	1983	AML	Not approved
Methotrexate	1987	Osteosarcoma	Approved as supplement
Teniposide	1990	ALL	Approved

Abbreviations: FDA, Food and Drug Administration; DNA, New Drug Application; ALL, acute lymphoblastic leukemia.

Lilly resubmitted data in 1982 from a phase II/III study conducted by the Children's Cancer Group (CCG) in patients with relapsed ALL. Of 228 patients enrolled, 55 patients were deemed vincristine resistant and evaluable. The response rate was originally reported as 33% (13 complete responses [CR] and three partial responses [PR]), but was subsequently found to be only 13% when a minimal duration of 4 weeks could not be confirmed in nine patients. The median response duration was 8 weeks. The median survival for responding patients was 4.5 months. Data on the median survival of the entire cohort of treated patients were not provided.

Although the FDA once again did not recommend approval based on the short response duration and unclear survival benefit, the ODAC recommended approval of the claim by a vote of 4 to 2. The FDA did not follow the split ODAC vote and did not approve the NDA. Published studies in children with ALL showed no improvement over the use of vincristine and showed greater toxicity with vindesine.[7,8] The sponsor subsequently did not pursue another marketing application.

Daunorubicin for Acute Leukemia

An NDA for daunorubicin was originally submitted by Ives Laboratories (New York, NY) for use in pediatric and adult ALL and AML. After presentation before the ODAC in 1979, daunorubicin was approved for adult AML. The sponsor subsequently submitted a supplemental NDA for pediatric ALL that was approved in 1983. The records from this submission were unavailable for review. Another supplemental application for daunorubicin in adult ALL was approved by the FDA in 1987.

Table 4. Effect of Incentive Program on Pediatric Oncology Drug Development as of May 2002

	CDER	Oncology
Proposed pediatric study requests (PPSR) received	~300	18
Total written requests issued	~250	25
Written requests issued without a PPSR	~50	13
Written requests issued for approved products	~190	12
Study reports submitted	65	1
Exclusivity granted	57	1
New pediatric labeling	34?	1

Abbreviation: CDER, Center for Drug Evaluation and Research.

Teniposide for Neuroblastoma

The pivotal studies submitted by Bristol-Myers Squibb (Princeton, NJ) consisted of two uncontrolled, nonrandomized phase II studies—one from the CCG and a second from St. Jude Children's Research Hospital.

Thirty-four patients with disseminated disease refractory to conventional regimens were treated with teniposide as a single agent in a CCG study. Only 24 patients were considered evaluable for efficacy. The overall response rate was reported as 33% (one CR, seven PR). The median response duration was 10 weeks (range, 4 to 30+ weeks). A cohort of 20 patients treated with one of four potential single- or multiagent regimens not containing teniposide served as historical controls. No responses were observed in this group.

The St. Jude study involved 14 patients with refractory, disseminated disease who were treated with teniposide. Data from 24 patients treated with vincristine with or without the addition of dacarbazine were submitted as a historical control; however, only nine patients in each group were considered evaluable for efficacy. The overall response rates were 33% (three PR) for teniposide versus 11% (one PR) in the historical controls. The median response duration for teniposide-treated patients was 3 to 4 weeks.

The FDA review concluded that this submission did not contain adequate and well-controlled studies and was not approvable. The reasons for this decision included the absence of any randomized studies and inappropriate historical control groups. The multitude of treatment regimens in the CCG historical control group suggested potential heterogeneity. In the St. Jude study, evolving standards of therapy may have unfavorably biased the historical cohort because several patients were treated more than 7 years before the initiation of the teniposide trial. In addition, the selection of response rate as the primary efficacy end point was viewed as inadequate for the evaluation of treatment efficacy because no correlation with clinical benefit (eg, prolonged survival time, reduced relapse probability, or improved quality of life) was demonstrated. Finally, the small number of evaluable patients and responders from either study limited statistical confidence in the results. This NDA was not presented to the ODAC.

5-Azacytidine for AML

Upjohn (now Pharmacia & Upjohn, Peapack, NJ) submitted an application for 5-azacytidine for the therapy of AML, consisting of five studies. Four of these studies were uncontrolled phase II trials in adults with AML that was resistant to conventional therapy. The remaining study was a phase II pediatric trial conducted by the CCG (CCG A020). Children with resistant disease in this trial were induced with intravenous 5-azacytidine at 100 to 300 mg/m^2 on a schedule of once a day for 5 days. The initial analysis consisted of eight patients with an overall response rate of 25%. The FDA concluded that the small number of pediatric patients and the lack of survival data in this uncontrolled study rendered the pediatric data inconclusive to support approval.

The ODAC, in voting 5 to 2 against approval for remission induction in adults or children, emphasized that despite strong indications of activity in this disease setting, the lack of adequately controlled studies precluded determination of clinical benefit.

The sponsor resubmitted data in 1983 that included the results from historical controls from selected adult studies. For the pediatric indication, updated information from the CCG and data submitted as an abstract from a study at Memorial Sloan-Kettering Cancer Center were submitted. The CCG study now included 11 patients, of whom 45% had responses. The median remission duration was 20 weeks. The published abstract described 30 adult and pediatric patients with a variety of solid tumors and leukemias.[9] Within this group, there were nine children, and seven patients with ALL; however, the number of pediatric patients with ALL was not specified. A single PR was reported in a child with ALL.

For reasons similar to those cited initially, the FDA did not view these supplemental data as adequate for approving a claim regarding 5-azacytidine in either children or adults. Although the FDA was willing to accept a historically controlled trial as supportive evidence, it was reluctant to accept a historical study as primary efficacy evidence. The reasons cited for nonapproval of pediatric indications included uncontrolled studies, limited numbers of evaluable patients, and absence of survival data. A review published in 1987 noted the 20-year clinical experience with 5-azacytidine and the lack of data supporting a specific role in leukemia therapy.[10]

Methotrexate for Osteosarcoma

An sNDA submitted by Lederle Laboratories (now Wyeth-Ayerst, Philadelphia, PA) was intended to support the contribution of high-dose methotrexate for the treatment of osteosarcoma.

Initially, the sponsor submitted three randomized, controlled prospective trials in which high-dose methotrexate-containing adjuvant regimens were compared with observation in patients who had either tumor resection or limb amputation.

Pediatric Oncology Group (POG) 8107 enrolled 113 patients, of whom 36 accepted postoperative random assignment to either observation or a 43-week long regimen that included high-dose methotrexate with leucovorin rescue, bleomycin, cyclophosphamide, dactinomycin, doxorubicin, and cisplatin. A significant difference ($P = .001$) was observed in the median disease-free survival (DFS) between the observation (157 days) and the adjuvant therapy arm (median DFS not reached). The relapse rates were 83% and 39% in the observation and adjuvant therapy arms, respectively; however, no significant difference in overall survival was reported in the randomized patients. Of the 77 patients who refused random assignment, 18 chose observation and 59 chose adjuvant therapy. The results of this cohort of patients proved similar to that of the randomly assigned group with regard to relapse rate and overall survival.

Study 32–25-1, conducted at the University of California–Los Angeles (UCLA), the University of California–Davis, and the University of Oregon, reported on 56 patients randomly assigned to adjuvant therapy versus observation after preoperative intra-arterial doxorubicin. The adjuvant arm consisted of a 24-week regimen including high-dose methotrexate, leucovorin, vincristine, doxorubicin, bleomycin, cyclophosphamide, and dactinomycin. The FDA requested that the sponsor reanalyze the study after discrepancies in the randomization process and efficacy

calculations were noted during a compliance audit. On reanalysis, a significant difference ($P = .02$) remained in the median DFS in the observation arm (219 days) versus the adjuvant treatment (467 days). A borderline statistically significant difference ($P = .06$) remained in the median overall survival between the two arms, favoring postoperative chemotherapy.

Study 32–27-1, conducted at the Mayo Clinic, enrolled 87 patients, of whom 41 were randomly assigned to observation or to a 1-year adjuvant regimen of high-dose methotrexate, leucovorin, and vincristine. Significant differences in relapse rate, median DFS, and median overall survival were not seen; however, the trial was underpowered to detect a survival difference and did not achieve its accrual target.

The determination to recommend approval of methotrexate was based on a single phase II study. This study was not designed to evaluate the contribution of high-dose methotrexate in a multidrug regimen. Supportive efficacy evidence came from additional uncontrolled studies.

The FDA review recommended approval of this NDA. Because of deficiencies in study conduct and statistical analysis, the UCLA study was not considered an adequate and well-controlled trial for support of the NDA. The POG study was not designed to and did not determine the high-dose methotrexate contribution to the combination regimen. However, substantial published data from uncontrolled studies summarized in the NDA review demonstrated that high-dose methotrexate was effective in causing tumor regression in patients with metastatic disease and in causing tumor necrosis in patients who received preoperative chemotherapy. This provided evidence to support the efficacy of high-dose methotrexate in the treatment of nonmetastatic osteosarcoma.

The ODAC concurred with the FDA analysis and recommended approval of the claim in this supplemental NDA by a 10 to 0 vote. The definitive benefit of methotrexate to regimens containing cisplatin and doxorubicin remains unclear, illustrating the difficulty of reliably ascertaining the contribution of single agents used in multiagent regimens.[11]

Teniposide for ALL

After the FDA decision to not approve the NDA for teniposide in neuroblastoma, Bristol-Myers Squibb (Princeton, NJ) submitted a second application for teniposide for use in pediatric ALL. Data from four trials were submitted to support three ALL indications: consolidation therapy in second remission, induction therapy for primary induction failures, and induction therapy in refractory disease or in multiply relapsed patients.

The St. Jude R4 study was submitted to support the first indication. This phase III study randomly assigned patients to consolidation with teniposide (165 mg/m^2 intravenously twice weekly for 2 weeks) and cytarabine or to observation after successful reinduction. A total of 64 patients were randomly assigned from 1976 to 1979; 57 patients were evaluable. A difference in median duration of second remission was observed for consolidation treatment (21 weeks) versus observation (12 weeks; $P = .091$). A survival difference was not observed: 46 weeks for patients in the consolidation cohort versus 50 weeks for patients in the control cohort.

In support of the second indication, two uncontrolled phase II studies from St. Jude and the Dana-Farber Cancer Institute were submitted. Twenty-eight patients who had failed induction with standard agents were entered from 1975 to 1987. The induction regimen combined teniposide (165 mg/m^2 intravenously twice weekly for 4 weeks) and cytarabine (300 mg/m^2 on the same schedule). Patients who achieved CR were then treated with mercaptopurine and methotrexate or individualized therapy. For 25 evaluable patients, the CR rate was 56%, with a median duration of 13 weeks and a median survival of 37 weeks. The St. Jude results are summarized in several publications.[12-14]

A separate, uncontrolled phase II study from St. Jude was submitted to support the third indication. Eligible patients had a third relapse on prior St. Jude protocols (Total IX, R4, or R5). Only 25 of the 60 patients entered between 1978 and 1980 were evaluable. Prior teniposide exposure was the most common reason for patient ineligibility (63%). The CR rate among these 25 patients was 20%. Among responders, the median survival was 55 weeks.

In addition to the submission of a single primary efficacy study in support of each proposed indication (of which studies only one was a controlled phase II study), the FDA cited common problems among all of the submitted studies. These included retrospective data collection and analysis by the sponsor; complex regimens, none of which isolated the contribution of teniposide to efficacy; poor compliance with the original statistical plan; and multiple protocol violations. The latter consisted of additional or substitute therapies not specified in the protocol that were administered to patients in all three studies. The FDA review concluded that the first and third indications were not approvable, but that the 4-month duration of second remission demonstrable in patients failing primary induction was sufficient for approval.

In July 1991, the ODAC recommended against approval for all three indications by votes of 9 to 0, 5 to 4, and 7 to 2, respectively. Given the dichotomous voting for the second indication, the FDA requested the sponsor to provide further data to document patient refractoriness to drugs used in combination with teniposide. After submission of additional data on 25 patients, the FDA confirmed the CR rate was 24% with a response duration ranging from 6 weeks to 13 years. These data were deemed adequate to support approval of teniposide in induction therapy in children with refractory ALL in combination regimens.[15]

DISCUSSION

During the last 20 years, there have been six submissions to the Division of Oncology Drug Products of the CDER of the FDA for pediatric oncology indications. Three of these submissions were approved—two supplemental indications for drugs approved for adults and one new molecular entity, teniposide, for the reinduction of refractory ALL in combination with other active drugs. The last approval occurred in 1990.

To support approval for a pediatric claim, submissions to the FDA are considered favorably if they contain controlled studies of adequate size with disease-appropriate end points, a treatment regimen that can be applied to clinical practice, and prospective data collection with a prospective analysis plan. These characteristics should permit unbiased demonstration of a new drug's contribution to efficacy.

In the applications that did not lead to approval there were several common features. These included the absence of well-controlled studies (vindesine, teniposide, 5-azacytidine), use of inappropriate controls (teniposide for neuroblastoma), patient heterogeneity (teniposide for neuroblastoma), short response duration (vindesine), and small number of patients (teniposide, 5-azacytidine). Additional reasons relating to nonapproval were the use of an unvalidated surrogate marker (teniposide for neuroblastoma), difficulty in applying the findings to clinical practice (vindesine), and the use of complex regimens that do not indicate the contribution of the new drug to efficacy (teniposide for induction of ALL).

The Code of Federal Regulations has a requirement for adequate and well-controlled studies. The submissions for methotrexate, 5-azacytidine, teniposide, and vindesine all contained uncontrolled or historically controlled studies. Historical controls may not reliably determine therapeutic efficacy. Changes in the standard of care or supportive measures may bias the results in favor of the most recent cohort if a substantial time interval exists between the treatment period for a study cohort and the historical controls. Furthermore, the inclusion of more than one treatment regimen in the historical control group can severely limit and complicate interpretation of the historical comparison, such as in the case of methotrexate for osteosarcoma.

The use of inadequately designed or underpowered studies can be complicated by poor protocol compliance and a high level of patient ineligibility that results in few evaluable patients, as in the cases of teniposide for neuroblastoma or 5-azacytidine for AML. Small numbers of patients or heterogeneity in the patient population do not allow statistical analysis of the results, as in the cases of teniposide for neuroblastoma and ALL, methotrexate for osteosarcoma, 5-azacytidine for acute leukemias, and vindesine for ALL.

The general principles of cancer drug registration are demonstration of clinical benefit in a defined population; demonstration of the effect of the test drug by replication of the findings, usually by demonstration of the clinical benefit in at least two clinical trials; and adequate safety data to assess risk and benefit in a defined population. The conventional approach to obtaining a marketing license for a new drug is to perform two or more studies designed to establish clinical benefit directly. End points that are commonly considered proof of clinical benefit are survival or the diminishing of disease-related symptoms.[16]

An alternative strategy is to seek accelerated approval as described under Subpart H of the Code of Federal Regulations, 21 Section 314.[17] Under this provision, improvement of a surrogate marker likely to predict clinical benefit for a serious or life-threatening disease that has no satisfactory available therapy could lead to approval. Examples of diseases that represent unmet medical needs in pediatric oncology include glioblastoma multiforme, brainstem gliomas, infant leukemias, and relapsed metastatic sarcomas. The approval mechanism mandates subsequent studies to directly demonstrate clinical benefit.

The Subpart H approval mechanism allows a planned interim analysis of a randomized controlled study with a clinical benefit end point. The interim analysis could examine a surrogate end point such as response rate and could be used to support accelerated approval with the demonstration of clinical benefit to follow.

In addition, accelerated approval has been granted in single-arm trials examining response rate in unmet medical need conditions. Recent examples of accelerated approval include irinotecan (Camptosar; Pharmacia & Upjohn, Peapack, NJ) for relapsed or refractory colorectal cancer, temozolomide (Temodal; Schering-Plough, Kenilworth, NJ) for refractory anaplastic astrocytoma, and imatinib mesylate (Gleevec; Novartis, East Hanover, NJ) for chronic myelogenous leukemia in blast or accelerated phase.

The FDA continues to be concerned about the paucity of pediatric submissions for oncology. Since 1979, regulations have been issued to address the general issue of the lack of adequate labeling of drug products for children.[18]

In 1994, the FDA issued a regulation (the 1994 Final Pediatric Rule) that allowed efficacy data from adult studies to be extrapolated to pediatric populations if the disease or condition under study existed in both the pediatric and adult populations and if the therapeutic response was similar.[19] The intention was to encourage sponsors to develop drugs in pediatrics and to provide pediatric information for drug labeling for both marketed drugs and new molecular entities under regulatory evaluation. Specifically, the provision permits the information from adequate and well-controlled adult studies to support a pediatric indication. Additional pediatric information, such as appropriate pediatric dosage (eg, pharmacokinetic data) and pediatric safety information must also be submitted.

The response to the initiative was less than anticipated, prompting both a mandate (the Final Pediatric Rule of 1998) and an incentive program under the Food and Drug Modernization Act of 1997. The application of the Pediatric Rule of 1998 is based on the principle that an adult indication under review is similar to a pediatric disease or condition.[20] The application of the 1998 Rule to pediatric oncology was a subject of ongoing discussions of the Pediatric Oncology Subcommittee of the ODAC.

The incentive program outlined in Section 111 of the FDA Modernization Act of 1997 (FDAMA) was intended to address the situation both when a pediatric disease is the same as in the adult indication and also when it is different, when extrapolation of data is not possible.[21] The incentive is a 6-month extension to marketing exclusivity based on existing patent or other marketing exclusivity and applies to the entire product line, independent of indication or dosage form, of an active chemical moiety. It can be granted if a study report fairly responds to a FDA-generated Written Request. A Written Request may be initiated by a proposal submitted to the FDA from a drug sponsor or other party with the permission of the drug sponsor, or it may be initiated internally by the FDA. It may be granted regardless of study outcome (ie, a negative study may qualify, because the intent is to provide appropriate pediatric information). Drugs under development as well as currently approved drugs may receive a Written Request. The law did not permit the incentive to apply to biologicals, selected antibiotics, or devices.

The Division of Oncology Drug Products has interpreted the incentive program to allow a pediatric oncology development plan to qualify for determination for an exclusivity extension even when a specific pediatric indication is not targeted.[22] If a sponsor submits data from an adequate phase I and specified phase II studies in response to a FDA Written Request, a

determination for an exclusivity extension may be requested. In the unusual circumstance that a drug is prohibitively toxic for continuing development beyond phase I trials, a request to the FDA for a pediatric determination exclusivity may be made after the phase I studies. Completion of phase II studies, irrespective of a demonstration of efficacy, may lead to granting of an exclusivity extension. If the results of phase II studies are promising in a disease that is life threatening and for which no effective therapy exists, then a sponsor may apply for accelerated approval using a surrogate marker under Subpart H of the Code of Federal Regulations 21 Section 314.510. Drugs that exhibit evidence of activity would be expected to be developed in phase III studies, although this may not be a condition for granting pediatric exclusivity. A guidance document and sample written request template are posted on the FDA Web site at www.fda.gov/cder/cancer.[23] The incentive program associated with FDAMA expired on December 31, 2001. On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) was signed into law.[24] The BPCA has a new incentive program that retains most of the features of the FDAMA initiative. The BPCA has several additional features, including a program to study off-patent drugs and an emphasis on dissemination of pediatric information through product labeling and other mechanisms. The BPCA incentive program expires in 2007.

As of December 2002, the FDA received 18 proposals for pediatric oncology studies and had, in addition, issued unsolicited written requests. Not all proposals for pediatric studies resulted in a written request. More than 25 written requests for oncology products were issued, of which 14 were for approved products and the remainder were for products under development. Four products have submitted the requested study reports, and pediatric exclusivity was granted. Overall, the FDA has issued more than 260 Written Requests, with more than 75 pediatric exclusivity determinations made and more than 60 granted.[25]

The FDA has a desire to be flexible and practical in accepting data intended to support a marketing claim. It should be noted that studies performed outside the United States have been used to support domestic approval and may be acceptable for a pediatric study report. The FDA recommends discussion with a pediatric cooperative group to use their expertise and resources to assist with study design and patient accrual and further recommends meeting with the FDA to review the specifics of any proposal.

The intent of the FDA pediatric initiatives is to stimulate the development of new therapeutics for pediatric indications and to encourage the submission of quality clinical data. These initiatives are only part of a larger matrix to provide new therapies for pediatric oncology patients.[26] The FDA has established a Pediatric Subcommittee of the ODAC, incorporated additional pediatric oncologists in the review staff, and established a new Office with responsibility to coordinate and facilitate pediatric drug development. Additional initiatives that may facilitate the initiation of studies in pediatric patients with cancer include the following: the pharmaceutical industry consortium of pediatric oncologists; greater coordination and cooperation between the Children's Oncology Group and the pharmaceutical industry; involvement of patients, patient families, and patient advocacy groups in all phases of development; and the development of predictive preclinical models.

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