C L C CANCER LEADERSHIP COUNCIL

A PATIENT-CENTERED FORUM OF NATIONAL ADVOCACY ORGANIZATIONS ADDRESSING PUBLIC POLICY ISSUES IN CANCER

June 5, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, Maryland 20857

Re: Docket No. 00N-1266
[Request for Comments on Pediatric Exclusivity]

To Whom It May Concern:

The following comments on the pediatric exclusivity program are submitted on behalf of the undersigned organizations representing people with cancer, their caregivers and cancer research organizations. Although some of our organizations are specifically dedicated to advocacy on behalf of children with cancer, we view the pediatric exclusivity program as a critical experiment in the ongoing effort to offer appropriate incentives to private entities to stimulate research for relatively small numbers of patients. Most cancers qualify as orphan diseases, and therefore the impact of this program as a stimulus for private research in cancer is of special interest to us.

Unfortunately, to date, we have been disappointed that the program has been virtually ineffective for childhood cancers. While the leadership of the Oncology Products Review Division of the Food and Drug Administration (FDA) has made extraordinary efforts to render the pediatric exclusivity incentive meaningful for pediatric cancer, the agency's interpretation of the statute has not taken into account the special circumstances of pediatric cancer. The result has been that children with cancer have not benefited from an important private inducement to fund pediatric cancer research that could yield important information about the treatment of pediatric cancer. We seek to work with FDA and others to encourage a more flexible and rational approach to implementing this incentive and to developing other strategies to improve treatments for childhood cancer.

**The Statute**

Section 111 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) provides an additional six months of marketing exclusivity either to sponsors of new—i.e., unapproved—drug applications, or to sponsors of "already marketed" drugs, if the sponsors carry out pediatric studies requested by FDA that "may produce health benefits in the pediatric population." This six-month extension of exclusivity covers all uses of a drug and thus offers a fairly significant incentive.

A second six-month period of exclusivity is available "for a supplemental application" for a drug that has already received the first six months, if the sponsor otherwise complies with the requirements of

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carrying out requested studies. This second exclusivity period is less significant because it covers only the indication referenced in the supplemental application.

A central feature of the legislation is the requirement that the Secretary, after consultation with experts in pediatric research, develop a prioritized "initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population." The list was required to be published no later than six months after enactment.

The pediatric exclusivity program under Section 111 sunsets January 1, 2002. The Secretary is required to report to Congress no later than January 1, 2001, about the experience under the pediatric exclusivity program, including the following issues specified by Congress:

> (1) the effectiveness of the program in improving information about important pediatric uses for approved drugs;
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> (2) the adequacy of the incentive provided under this section;
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> (3) the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients; and
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> (4) any suggestions for modification that the Secretary determines to be appropriate.

**Comments**

Consistent with the statutory instruction to prepare a report to Congress, FDA's Request for Comments is seeking views of interested parties on four topics:

> **1. Effectiveness of the program in improving information about important pediatric uses for approved drugs.**
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> **The program has been ineffective in improving information about drugs used in pediatric cancer, since little research in pediatric cancer has been stimulated.**
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> The statistics speak for themselves. Current FDA data indicate that the agency has issued only two written requests for pediatric cancer studies to date, and these came after almost a year of aggressive advocacy by pediatric cancer advocates. Further, industry has made only five efforts to obtain pediatric exclusivity over the two-and-a-half years in which the statute has existed. These disappointing results clearly indicate that the program has failed for pediatric cancer unlike its success in other disease indications.
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> We believe that the pediatric exclusivity program has failed for children with cancer because of a series of overly restrictive interpretations and actions by the FDA, which are described below. We believe it is essential that greater industry resources are allocated to timely and effective research on pediatric cancer. Accordingly, we are committed to working with industry, FDA, NCI and the pediatric oncology community to ensure that innovative, high quality clinical trials in pediatric cancer result in the eradication of these diseases and would urge FDA reconsideration of its interpretation of Section 111 in the case of pediatric cancers.

a. FDA, in interpreting the statute, has imposed requirements not intended by Congress and not provided for in the statute.

Section 111 requires only that sponsors agree to requested studies that "may produce health benefits in the pediatric population." Rather than requesting pediatric studies proposed by pharmaceutical sponsors in consultation with experts in pediatric cancer research, it is our understanding from industry representatives that FDA has in effect imposed the complications, delay and expense of filing a new drug application (NDA) or supplemental new drug application (SNDA).

FDA currently maintains that an NDA or SNDA is not an explicit requirement to qualify for exclusivity. However, the "Pediatric Cancer Therapeutics: Letter of Interest" posted on the FDA website indicates that, to obtain pediatric exclusivity for oncology drugs, a sponsor must commit to studies effectively leading to an NDA or SNDA. Congressional sponsors of the legislation that became Section 111 have confirmed to patient advocates, and we believe to FDA as well, that the requirement of filing an NDA or SNDA was not intended by Congress nor supported by the statutory language.

FDA's basis for imposing additional requirements on sponsors seeking pediatric exclusivity seems to be a reference in the statute to the fact that studies, after the request has been issued by FDA, must be "reported in accordance with the requirements of the Secretary for filing." Because NDAs and SNDAs must be "filed," FDA takes the position that the requirements for NDAs and SNDAs are to be superimposed on Section 111, which features no such requirements. This statutory construction ignores the fact that the concept of "filing" appears numerous times in the Act with almost no overlap in meaning.1 The only consistency is that, wherever "filing" is mentioned, it is in accordance with the common language meaning of the word, which is to submit a package of information to an agency or other recipient. Reference to "filing" in Section 111 cannot, standing alone, reasonably result in imposition of the entire set of responsibilities accompanying NDAs or SNDAs.

Additionally, when the drafters of Section 111 intended to impose SNDA requirements, they did so explicitly, in contrast to the above reference to "filing." Elsewhere in Section 111, a second six-month exclusivity period can be awarded for sponsors who successfully file a "supplemental application." Rules of statutory interpretation dictate that, if a requirement is specifically mentioned in one part of a statute but omitted from another, the omission cannot be ignored. Moreover, if a supplemental NDA must be filed in connection with the first set of studies, which theoretically results in six months additional exclusivity, the second exclusivity period appears to be rendered meaningless. It is also a rule of statutory construction that a statute should be interpreted so that every part of it is given effect.

FDA's interpretation of the statute in this manner has real consequences for pediatric cancer. A disease like cancer, where the course of the disease is likely to be different in adults and children, is effectively discriminated against as a result of FDA's interpretation. Congress intended to stimulate private sector investment equally across all diseases by offering incentives for pediatric studies that "may produce health benefits" for drugs used in children. However, requiring pediatric studies of cancer drugs to meet NDA or SNDA standards for

cancer drug approvals effectively imposes highly burdensome requirements. We believe that this interpretation has dampened industry interest in taking advantage of the incentive.

b. FDA's interpretation of the statute has not taken account of the standards and practices of pediatric oncology research.

To make the incentive meaningful for childhood cancer, FDA should have implemented the pediatric exclusivity provision after thorough consultation with experts in the pediatric oncology community. Decisions about the priority of clinical trials for pediatric exclusivity purposes through Section 111 should be based upon advice by "experts in pediatric research," as the statute requires. Their input would have increased the chances that the exclusivity program would have yield a greater number of appropriate studies for pediatric cancer with the result that children with cancer would benefit from the incentive.

The successes in treating childhood cancer over the past 15-20 years have been accomplished independently of FDA's labeling requirements. Drugs used to treat pediatric cancer are approved for the treatment of cancer in adults. These drugs are then evaluated through NCI pediatric cooperative group and cancer center studies and used off label for cancer in children. Pediatric oncologists regard the initial approval of an oncology drug or biological product as a license to use it in practice, guided by the considerable peer-reviewed literature reporting clinical studies. Advances in cancer therapies proceed by the rapid translation of new scientific findings into clinical practice. The practice of pediatric oncology, which is responsible for real and dramatic increases in survival rates over the past two decades, should be enhanced by the availability of Section 111 and not hindered by delays inherent in the process of reviewing NDAs and SNDAs.

Pediatric oncologists have openly stated that, for many compounds in current use, dosing and side-effects data would add significant information that would improve the treatment of children with cancer. However, such data, by FDA's current process, could be gathered only as part of a development plan to obtain a labeled indication for a drug, i.e., full approval. Full approval would require efficacy trials according to FDA's usual adult standards, where the incidence and type of disease are very different from pediatric cancer. Even when a drug is known to be effective based on studies by the pediatric oncology cooperative groups, FDA seems to be requiring additional efficacy studies. Obtaining exclusivity for drugs in current use is especially problematic because of the nature of the efficacy trials FDA usually requires for NDA or SNDA purposes—e.g., single agent studies to show the individual contribution of a compound. Such studies are likely be unethical in pediatric cancer because it has been well established that no single agent alone is expected to show efficacy in this disease setting. Pediatric "gold standard" efficacy trials, which have established the standard of care through the pediatric oncology cooperative groups, typically do not satisfy FDA's approval standards.

Greater industry funding in pediatric cancer could offer new hope for childhood cancers for which treatment advances have lagged. New approaches are desperately needed for pediatric solid tumors, including most types of brain tumors. Pediatric oncologists desire access to promising new agents, which are most often developed by industry. Section 111 offers a targeted incentive that could stimulate studies in these difficult to treat pediatric cancers. However, FDA requirements that studies be sufficient for labeling undermine the potential of the incentive for industry to study these diseases.

c. FDA delays and inconsistencies in implementing the pediatric exclusivity program for pediatric cancer have further undermined its potential.

FDA development of the mandated "list" has been characterized by inconsistencies and delays that have been especially disadvantageous for pediatric cancer. The first list published by the agency in March 1999 contained a substantial number of cancer drugs targeted for pediatric studies. However, in May 1999, the agency issued a replacement list that contained only a few relatively marginal drugs, apparently based on its conclusion that the list should include only drugs where the disease was the same in adults as in children. This requirement unduly limits studies of drugs that might yield benefits for children.

Timely consultation with pediatric oncology research experts could have created a meaningful list of priority drugs for study in pediatric cancer and would have increased the pace of pediatric cancer research. At present, there is no meaningful list of cancer drugs that might be studied for the purpose of demonstrating health benefits in children. Further, to the confusion of many, the agency has maintained that the list is only an internal tool for determining how the agency's resources should be employed rather than a list of priorities, as the statute required.

Contrary to this view, the list mandated by Congress has a very important function outside of the government—that is, notifying private sector companies of research opportunities that may be eligible for the incentive of extended exclusivity. Absent the list, companies may not know the research opportunities and will not step forward to fund important projects.

d. FDA's interpretation has imposed unrealistic time lines on prospective sponsors and thus undermines the incentive for pediatric cancer research.

There have been additional barriers to the successful implementation of the exclusivity incentive. Data released by FDA do not disclose the average time required to navigate the process before a sponsor may receive a request for pediatric exclusivity studies. Anecdotal information from the trade press indicates that it may take well over a year before a sponsor is able to reach closure with the agency on the requirements necessary to obtain pediatric exclusivity.

After agreement with the agency and receipt of the formalized request, sponsors must then conduct studies—more than one as required in the NDA and SNDA process. With the small number of patients affected by different childhood cancers, such studies typically take three to four years.
Adding the time to negotiate with FDA on requirements for the studies, a sponsor would face about five years to qualify for exclusivity. It is important to note that the entire period of exclusivity available to a new drug (without patent protection) under the Hatch-Waxman legislation is five years. Thus, by the current method of implementing Section 111, it seems practically impossible for such a drug to benefit from pediatric exclusivity—the original exclusivity will probably expire before FDA's requirements to study drugs in pediatric cancer can be satisfied.

**2. Adequacy of the pediatric exclusivity incentive.**

**As the statistics concerning pediatric studies stimulated by Section 111 clearly reflect, the incentive is inadequate in pediatric cancer.**

It is possible that six months additional exclusivity could be a significant incentive for sponsorship of pediatric research, in cancer as in other diseases, but only if the incentive is reasonably attainable. If the burdens imposed on prospective sponsors are perceived to outweigh the potential benefits to them, the incentive will not work.

Many believe that an incentive greater than six months might be necessary to increase industry involvement in pediatric cancer research. This perception may require further investigation for verification. However, regardless of the nature of the incentive, its implementation must be timely, efficient and consistent with the standards and practices of pediatric oncology.

**3. Economic impact of the pediatric exclusivity program on taxpayers and consumers.**

**There is a negative impact on the well-being and future productivity of childhood cancer patients who might have benefited, but little if any impact on taxpayers and consumers.**

The negative impact on the productivity and well-being of those children who would have been helped by advances in pediatric oncology research must be noted. There is broad consensus in the pediatric oncology community that incentives are necessary to stimulate much needed private sector research to hasten the development of effective treatments for childhood cancers.

As a test case, the Section 111 incentive has failed to generate progress in pediatric cancer research, and consequently failed to improve the potential of the lives of children diagnosed with cancer.

With respect to the impact on taxpayers and consumers, concern for the availability of generic drugs—even over an extension of only six months—is appropriate in most circumstances. However, patients facing life-threatening diseases understandably place a higher priority on incentives for research than on access to lower cost versions of drugs. Research may produce new and more effective therapies than lower cost drugs with known but modest impact.

In cancer therapies, whether for adults or children, the availability of generic drugs has little or no direct impact on consumers. The insulation of patients from drug pricing considerations flows from the fact that drugs are generally components of global payments made either to physicians or hospitals. Payments by, or on behalf of, patients are usually the same regardless of whether generic or innovator drugs are used.

With respect to taxpayer impact, the result is not much different. Current reimbursement systems for both physician and hospital administration of chemotherapy drugs do not distinguish between generic and innovator drugs. Thus, cancer patients as consumers or taxpayers typically do not gain an advantage by the earlier availability of generic alternatives.

**4. Suggestions for modification.**

**Specific recommendations for FDA action.**

Given the self-evident failure of the Section 111 incentives to benefit pediatric cancer, FDA should reconsider its interpretation in implementation of the statute by creating an exception for pediatric cancer studies (and possibly studies for other childhood life-threatening diseases).

**Specific recommendations for modifications will be forthcoming to Congress.**

We support reauthorization of the pediatric exclusivity incentive but with modifications that will make it meaningful for all pediatric diseases, and especially childhood cancer. Our understanding of the congressional intent in Section 111 was that it would provide an incentive, beyond FDA's regulatory authority in the "Pediatric Rule," to encourage private sector support for pediatric research. If the incentive of six months additional exclusivity is to be meaningful—at least for pediatric cancer—it must be independent of the discretion of FDA to add requirements or limitations that effectively undermine the incentive. Further, it must be implemented consistent with the general conduct of pediatric oncology research—a strategy that has yielded unprecedented advances in cancer treatment.

As the life-span of the statute draws to a close, Congress should consider legislative measures that either (1) restrict FDA discretion to limit the incentive, or (2) provide a separate incentive for childhood cancer and other life-threatening diseases, where research is sorely needed to improve treatment options and save the lives of children. We will provide specific legislative suggestions to the Congress.

**Cancer Leadership Council**

Alliance for Lung Cancer Advocacy, Support and Education
American Cancer Society
American Society of Clinical Oncology
Cancer Care, Inc.
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The Children's Cause, Inc.
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National Coalition for Cancer Survivorship
National Patient Advocate Foundation
North American Brain Tumor Coalition
Oncology Nursing Society
US-TOO International Inc.
Y-ME National Breast Cancer Organization

American Society of Pediatric Hematology/Oncology
National Childhood Cancer Foundation

**Footnote:**

1 Among other things, the Federal Food, Drug and Cosmetic Act (FFDCA) uses "filing" to describe the act of submitting not only supplements or new drug applications, but also the "filing" of petitions for nutrient content claims (§ 343), pesticide exemptions (§ 346a), food additives (§ 348), and dietary ingredients (§ 350b); reports regarding device safety or efficacy (§ 360i); and notices of claimed exemptions for open protocols (§ 360dd). Moreover, the FFDCA includes mention of "filing" petitions for judicial review in federal courts (§§ 333, 334, 355 et al.), "filing" of prescriptions by pharmacists (§ 353), and "filing" for bankruptcy by device manufacturers (§ 356c).