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Issue Brief

Balancing Safety, Effectiveness, and Public Desire: The FDA and Cancer

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Introduction

Cancer is the second leading cause of death in the United States, exceeded only by heart disease, and it is the leading cause of death among those 35 to 64 years of age. One of every four deaths is from cancer.[1]

The federal government has spent more than $46 billion on cancer research since President Nixon declared a War on Cancer and Congress passed the National Cancer Act in 1971. In addition, states, private companies, and foundations invest billions of dollars in research and the development of new therapies. This investment recently produced the first evidence of reduced mortality from cancer. Cancer deaths declined 6 percent between 1990 and 1999 after two decades of increase between 1970 and 1990.[2] The benefits have not been uniformly shared among all patient groups or cancer types.[3] Against the big cancer killers, such as lung cancer, there has been little progress.[4]

Cancer treatment typically consists of a combination of surgery, radiation, and chemotherapy. Developments in scientific understanding of the basic mechanisms of cellular biology and genetics are beginning to result in newer chemotherapeutic agents. These agents target specific cell receptors to slow or stop the growth of tumors instead of killing all cells undergoing rapid growth and proliferation, both malignant and normal.[5,6] A handful of drugs with more directed action are used in cancer therapy now, and over 300 new drugs are currently in clinical trials.[7] The new cancer biology presents opportunities and challenges to scientists and the Food and Drug Administration's review and approval process. Advances in cancer biology and treatment also raise questions regarding the role of the National Cancer Institute (NCI).

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Background

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services' Public Health Service, is responsible for regulating the safety and efficacy of drugs, vaccines, and medical devices. Its legislative mandate comes from the 1938 Federal Food, Drug and Cosmetic Act and the Public Health Service Act. In the development of new drugs, the term "preclinical" refers to all activities that take place before testing on humans begins.[8] Preclinical research involves developing potential anticancer agents and testing them on tissue cultures and animals to determine how they work, if they're safe for humans, and whether they produce effective pharmacological activity to justify further commercial development. During preclinical research and testing, most compounds evaluated are, for a variety of reasons, found to be unworthy of further consideration.[9] For those that merit further work, the results of the laboratory and animal testing are used to design a detailed protocol for eventual clinical trials in humans.

When a decision is made to go forward with human clinical trials, the sponsor must file an investigational new drug application (IND) to the Center for Drug Evaluation and Research (CDER) at the FDA.[10] Prior to the application, there often are discussions between the parties as the product is being developed.[11] When the IND has been reviewed and the FDA has concluded that the investigational drug is safe enough to be tested on humans, clinical studies on humans may begin. The purpose of Phase I clinical trials is to establish a maximum therapeutically safe dose. This concentration is used for Phase II trials to establish short-term safety and biological effectiveness. Phase III trials provide additional information on an agent's safety, dosing, and effectiveness in a larger number of subjects; help define a drug's overall benefit to risk ratio; and determine how its official labeling will be worded.[12] When these three phases are completed, the results are incorporated into a final application, called a New Drug Application (NDA), for marketing approval and submitted to CDER.[13] If the drug is shown to be safe and effective, the FDA will approve it; if the product is found not to be safe and effective, the FDA will postpone or deny approval.[14] The FDA has regulations and guidelines regarding the kinds of results expected from clinical testing for NDA approval.[15]

Challenges to Cancer Research and Development

Traditional Endpoints and Biomarkers

Standard endpoints for FDA approval of chemotherapeutic agents are tumor shrinkage and survival. Experts suggest that new chemotherapeutic agents may have effective anticancer properties but work against different endpoints than these traditional ones.[16] Advances in scientific knowledge also may challenge the design of Phase I and Phase II clinical trials.[17] Experts suggest that for newer drugs the safe and effective dose should be based on biological activity, potentially replacing traditional endpoints.[18] Reliance on the traditional endpoints may lead researchers to overlook potentially important agents. It also may lead the FDA to reject or delay application reviews and may increase research, development, and review costs. Some surrogate endpoints, or "biomarkers," have been developed to help screen agents in the preclinical and clinical phases of drug development.[19] Barriers to a wider use of biomarkers are the current state of scientific knowledge, the identification and testing of surrogate endpoints for effective use in preclinical and clinical trials, and validation for use in the FDA review process.

Financial Incentives

Targeted agents that intervene in earlier stages of cancer and rely on surrogate endpoints to demonstrate safety and effectiveness may require a longer time for clinical trials. Patent protection is currently defined as 17 years from patent filing, typically coinciding with the submission of a sponsor's IND to the FDA. Under current conditions, patent life may expire before FDA marketing approval is requested or granted.

Intra- and Inter-Agency Coordination

There is no single individual or group at the FDA charged primarily with keeping track of, expediting, and coordinating research regarding anticancer agents for use in adults. Experts suggest that as science progresses, linkages between centers at the FDA and other federal agencies will become more important in prioritizing research activities and ensuring faster approval, while maintaining the necessary safeguards.[20]

Special Considerations

Pediatric Cancer Research

Two issues arise with respect to pediatric cancers. First, little research is carried out on agents targeted at pediatric cancers in part because it is difficult to do Phase I trials in children. The Department of Health and Human Services guidelines do not allow research with greater than minimal risk and/or with small probability of benefit in children. Second, there is delay in using agents developed for adults in children because children are generally not included in clinical trials for drugs developed primarily for use in adults until the drugs have been fully evaluated in adults.[21, 22, 23] Moreover, drugs approved for use based on adult clinical trial data do not have labels for appropriate child treatment and dosing. Experts suggest that the absence of pediatric testing and labeling poses significant risks, including avoidable adverse reactions.[24, 25] In the early 1990s, the FDA implemented a number of largely voluntary measures to encourage the submission of pediatric labeling information:

- The Food and Drug Administration Modernization Act provides financial incentives to manufacturers who conduct studies in children. The law provides six months exclusivity to drug sponsors in return for conducting pediatric studies. This is typically called the "pediatric exclusivity" rule.[26]
- The FDA Pediatric Rule, effective in 1999, requires that manufacturers of certain drugs and biological products conduct studies to provide adequate labeling for the use of these products in children. The FDA can require pediatric studies of a new drug if the product is likely to be used in a "substantial number of pediatric patients" or would provide a "meaningful therapeutic benefit" to pediatric patients compared with existing therapies.[27]
- The Best Pharmaceuticals for Children Act (BPCA), enacted by Congress in January 2002 (P.L. 107-109), extends pediatric exclusivity. For drugs with FDA marketing approval for adult treatment, the law provides a specific process and timeline for the application and requires priority review of pediatric supplements by the FDA. The BPCA established an office of pediatric therapeutics within the FDA to oversee pediatric activities within the agency.[28]

As of December 2002, 26 oncology drugs had been approved for study under the pediatric exclusivity rule. No significant changes in pediatric labeling had occurred.[29]

In 1999, the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and the Consumer Alert filed a citizen's petition with the FDA, challenging the FDA's legal authority to enforce the Pediatric Rule under the Food, Drug and Cosmetic Act.[30] The FDA denied the petition in 2000. A suit challenging the FDA's legal authority to enforce the Pediatric Rule was brought against the FDA in the federal district court of the District of Columbia by the same plaintiffs later in 2000. On October 18, 2002, the district court overturned the Pediatric Rule, finding that it went beyond the agency's statutory power.

Uncommon Cancers

Several adult cancers are underresearched due to significant barriers posed by financial considerations. In general, smaller markets for drugs with more precisely defined patient populations make these agents less attractive for big pharmaceutical companies.[31] How unattractive they are depends on the price companies may charge in the market. In the case of cancer, the price commanded by a drug may be high. The Orphan Drug Act, enacted in 1983, gave the FDA authorization to promote the development of drugs for rare conditions through the granting of an additional seven years of exclusive marketing for orphan products and tax credits for research undertaken to generate required data for marketing approval.[32] To date, more than 1,000 orphan products have been designated and more than 200 approved for marketing. Of these, 31 have been approved for cancer.[33]

Intellectual Property

Intellectual property issues may limit the availability of experimental drugs to both researchers and patients. Lack of agreement on intellectual property rights may stop or significantly delay preclinical and clinical research. Private companies typically do not want to let academic researchers study new agents for possible uses other than those being tested in a trial before the drug is approved in case some intellectual property is discovered. In addition, an evolving understanding of cancer biology implies that

new chemotherapeutic agents may be used in combination with existing drugs and other treatments to improve success rates. In order to identify and validate combination chemotherapy, preclinical and clinical trials testing agents in combination with others are required. To date, few such tests have begun. It is difficult for researchers to obtain nonapproved drugs to test in combination with other therapies for industry clinical trials or for trials sponsored by academic research centers because any safety problems encountered may lead to both drugs being withdrawn. The FDA does not have general guidelines in place to assess combination therapies for the IND and NDA review process.

The Role of the National Cancer Institute

The National Cancer Institute (NCI) is part of the National Institutes of Health (NIH) in the Department of Health and Human Services. The NCI is more involved with drug development than other NIH institutes.[34] This arose historically from uncertain corporate interest in this activity due in part to the financial and intellectual property issues discussed above and inadequate capacity of academic and commercial laboratories to perform all associated functions adequately. Since private companies and academic researchers have increasingly undertaken preclinical cancer research, some have questioned the role of the NCI in preclinical drug discovery and development.[35]

The NCI also promotes the translation of novel scientific understanding to clinic-based cancer therapy. The NCI director and others suggest that there is work to be done in updating the agency's practices to accommodate new scientific discoveries and promote wider collaboration among academic and corporate laboratories. In particular, some have highlighted the importance of the cancer tissue registries and genetic databases maintained by the NCI for intramural and extramural cancer research.[36] Statistical research activities also may need to be expanded to capture the benefits of novel agents and explore the capacity of combination therapies to treat cancer.

Recent Legislation

In the 107th Congress, three bills were introduced addressing the FDA's general role in cancer treatment development.[37] The National Cancer Act of 2002, introduced as identical bills in the Senate (S.1976) and in the House (H.R. 4596), had broad bipartisan sponsorship. The legislation would amend the Public Health Service Act to fund prevention and treatment programs for the NCI, including research translating preclinical to clinical testing. Another proposal, also titled the National Cancer Act of 2002 (S. 2955), would amend the Public Health Service Act to emphasize the importance of pain and symptom management through the nation's cancer programs. This bill also permits the secretary of health and human services to award grants to hospitals and advocacy groups to educate cancer patients and their families about the availability of pain and symptom control medication.[38] Each was referred to committee and received no further action.[39]

In the 107th Congress, three bills were introduced addressing the legally challenged Pediatric Rule.[40] Identical bills were introduced in the Senate (S. 2394) and House of Representatives (H.R. 4730) in the spring of 2002. Another, similar bill, H.R. 5594, was introduced in the House. The legislation would have amended the Federal Food, Drug and Cosmetic Act to require that NDA applications submitted to the FDA include assessments of a drug's safety and effectiveness for use in pediatric patients. The legislation would have required pediatric labeling, including dosage information, for all new drug applications to the FDA. The bills permitted this information to be extrapolated from adult studies if the course of the disease and the effects of the drug are similar in all populations. The assessments could be deferred if the adult studies were completed earlier and the applicant submitted a plan for planned or ongoing pediatric studies. Under the legislation, the FDA would be required to grant a full or partial waiver of the pediatric data requirement for several reasons. The Senate Committee on Health, Education, Labor and Pensions reported S. 300 on October 8, 2002 (S. Rept. 107-300) with an amendment.[41] The amendment clarified the interaction of the Pediatric Rule and the pediatric exclusivity provision for drugs already approved for marketing by the FDA. For these drugs, the legislation required that, prior to the FDA invoking the Pediatric Rule, the FDA must ask the manufacturer to conduct pediatric studies voluntarily consistent with current FDA practice. The legislation received no further action.

Conclusion

The FDA faces challenges in balancing the need to ensure that drugs are safe and effective against pressure to make therapies available quickly. For life-threatening diseases such as cancer, the trade-offs may be particularly stark. In addition, the activities of the NCI may be reassessed to better meet the challenges and opportunities presented by developments in cancer research and treatment. Determining the proper balance for cancer research and the role of the private and public sectors will require ongoing attention by scientists and policymakers.

References

1 http://www.cdc.gov/nchs/data/nvsr/nvsr50/nvsr50_16.pdf/, accessed November 5, 2002.

2 CDC, *Health: United States, 2001,* available at http://www.cdc.gov/, accessed October 1, 2002.

3 P. S. Schein, "The Case for a New National Program for the Development of Cancer Therapeutics," *Journal of Clinical Oncology* 19 (June 15, 2001): 3142–53.

4 Up to 90 percent of childhood leukemias are now curable.

5 Although all cancers have in common the phenomenon of uncontrolled cell growth, they differ significantly in their cause, location, age of onset, susceptibility of population groups, severity, treatments, and aftereffects.

6 E. A. Sausville and J. I. Johnson, "Molecules for the Millennium: How Will They Look? New Drug Discovery Year 2000," *British Journal of Cancer* 83 (December 2000): 1401–04; K. A. Gelmon et al., "Anticancer Agents Targeting Signaling Molecules and Cancer Cell Environment: Challenges for Drug Development?" *Journal of the National Cancer Institute* 91 (August 4, 1999): 1281–87; E. A. Sausville and E. Feigal, "Evolving Approaches to Cancer Drug Discovery and Development at the National Cancer Institute, U.S.A." *Annals of Oncology* 10 (November 1999): 1287–91.

7 http://www.pharma.com/, accessed October 27, 2002.

8 http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf/, accessed November 4, 2002.

9 B. Randall IV, *The U.S. Drug Approval Process: A Primer.* The Congressional Research Service, The Library of Congress. June 1, 2001; Order Code RL30989.

10 http://www.fda.gov/fdac/features/2002/402_drug.html/, accessed November 4, 2002.

11 D. U. Vogt, *Food and Drug Administration: Selected Funding and Policy Issues.* Congressional Research Service, The Library of Congress. February 27, 2001; Order Code RS20033.

12 B. Randall IV, *The U.S. Drug Approval Process: A Primer.* The Congressional Research Service, The Library of Congress. June 1, 2001; Order Code RL30989.

13 http://www.cder.gov/, accessed October 27, 2002; and M. E. Gluck, *Federal Policies Affecting the Cost and Availability of New Pharmaceuticals.* Prepared for The Kaiser Family Foundation, July 2002. Available at http://www.kff.com/, accessed October 22, 2002.

14 D. U. Vogt, *Food and Drug Administration: Selected Funding and Policy Issues.* Congressional Research Service, The Library of Congress. February 27, 2001; Order Code RS20033.

15 http://www.cder.gov/, accessed October 27, 2002; and M. E. Gluck, *Federal Policies Affecting the Cost and Availability of New Pharmaceuticals.* Prepared for The Kaiser Family Foundation, July 2002. Available at http://www.kff.com/, accessed October 22, 2002.

16 P. S. Schein, "The Case for a New National Program for the Development of Cancer Therapeutics," *Journal of Clinical Oncology* 19 (June 15, 2001): 3142–53; A. Schatzkin and M. Gail, "The Promise and Peril of Surrogate End Points in Cancer Research," *Nature Reviews—Cancer* 2 (January 2002).

17 Biomarkers Definitions Working Group, "Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework," *Clinical Pharmacology and Therapeutics* 69 (March 2001): 89–95; A. Schatzkin and M. Gail, "The Promise and Peril of Surrogate End Points in Cancer Research," *Nature Reviews—Cancer* 2 (January 2002).

18 Ibid.

19 Defined as measurable sign that may not in itself be a direct measurement of how a patient feels, functions, or survives, but nevertheless, is considered likely to predict therapeutic benefit. Definition from http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf/, accessed November 4, 2002.

20 Ibid.

21 P. J. Houghton et al., "Testing of New Agents in Childhood Cancer Preclinical Models–Meeting Summary."

22 Ibid.

23 M. Smith and P. T. C. Ho, "Pediatric Drug Development: A Perspective from the Cancer Therapy Evaluation Program of the National Cancer Institute," *Investigational New Drugs* 14 (1996): 11–22.

[24] http://www.fda.gov/cder/pediatric/reportcong01.pdf/, accessed November 4, 2002.

[25] Ibid.

[26] Ibid.

[27] Ibid.

[28] http://www.fda.gov/cder/pediatric/, accessed November 4, 2002.

[29] http://www.fda.gov/cder/pediatric/reportcong01.pdf/, accessed November 4, 2002.

[30] United States District Court for the District of Columbia. Memorandum Opinion on Civil Action 00-02898 (HHK) *Association of American Physicians and Surgeons, Inc., et al. v. United States Food and Drug Administration, et al.* Available at http://www.bna.com/, accessed January 10, 2003.

[31] http://www.phrma.org/newmedicines/, accessed November 18, 2002.

[32] http://www.fda.gov/orphan/index.htm/, accessed November 5, 2002.

[33] http://www.accessdata.fda.gov/scripts/cder/onctools/statistics/cfm#Status/, accessed November 5, 2002.

[34] All information contained in this section may be found at http://plan.cancer.gov/about/role.htm/, accessed December 5, 2002.

[35] E. A. Sausville and E. Feigal, "Evolving Approaches to Cancer Drug Discovery and Development at the National Cancer Institute, U.S.A." *Annals of Oncology* 10 (November 1999): 1287–91; J. I. Johnson, S. Decker, D. Zaharevitz et al., "Relationships Between Drug Activity in NCI Preclinical *In Vitro* and *In Vivo* Models and Early Clinical Trials," *British Journal of Cancer* 84 (May 18, 2001): 1424–31.

[36] http://plan.cancer.gov/, accessed December 12, 2002.

[37] http://thomas.loc.gov/, accessed November 2, 2002.

[38] http://thomas.loc.gov/cgi-bin/bdquery/D?d107:4:./temp/~bdaunG::|/bss/d107query.html|, accessed November 4, 2002.

[39] http://thomas.loc.gov/, accessed November 2, 2002.

[40] http://thomas.loc.gov/, accessed January 10, 2003.

[41] Ibid.