

STATEMENT BY

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**“HARNESSING SCIENCE: ADVANCING CARE BY ACCELERATING
THE RATE OF CANCER CLINICAL TRIAL PARTICIPATION”**

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

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INTRODUCTION

Mr. Chairman, Members of the Committee, I am Richard Pazdur, M.D., the Director of the Division of Oncology Drug Products (the Division) at the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA or the Agency).

Dr. Patricia Keegan, the Director of the Division of Therapeutic Biological Oncology Products at CDER, is accompanying me today to answer questions on biological products. Prior to coming to FDA, I was associated with the M.D. Anderson Cancer Center in Houston, Texas, for 11 years, where I was involved in patient care, cancer research, medical education, and administration.

Because of my prior experience with patient, academic, and scientific communities, I am acutely aware of how FDA's decisions and requirements can impact the public we serve. Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the Public Health Service Act, and related statutes, the government performs a vitally important role in helping to ensure that the medical products that patients and their health care practitioners rely upon are both safe and effective. These safeguards are particularly important for our most vulnerable citizens, those who are seriously ill.

I am pleased to share with you what our Agency is doing to accelerate the delivery of innovative cancer treatments to meet the needs of cancer patients and their families. Let me start by discussing the clinical trials required in FDA's new drug approval process and how patients gain access to these clinical trials. Our Division's mission within FDA is to ensure

that new cancer drugs are safe and effective and to facilitate access to promising therapies for seriously ill and dying patients when no other treatment is available. In my remarks, I will use the term “drug” to refer to both traditional small molecules and to therapeutic biological products.

Clinical Trials

Most clinical trials are carried out in steps called phases. Each phase is designed to gather different types of information. Patients may be eligible to participate in studies in different phases, depending on their general condition, the type and stage of their cancer, and what therapy, if any, they have already had. Patients are seen regularly by the investigators during the study to determine the effect of the treatment, and treatment is stopped if side effects become too severe.

The purpose of a Phase I clinical trial is to find the best way to administer a new treatment and learn how much of it can be given safely. In a Phase I study, a new treatment is given to a small number of patients. For a new drug, the study starts by giving a very low dose of the drug and the dose is then slowly increased as new patients enter the trial.

Phase II studies are designed to find out if a treatment has the intended effect. In the context of cancer therapy, Phase II studies are designed to study whether the treatment actually damages cancer cells or slows their growth in people. Usually groups of 20 to 50 patients with one type of cancer receive an investigational treatment in Phase II studies. For example, patients with breast cancer who no longer respond to standard therapy may choose to be treated in a Phase II study.

Patients are closely observed for anti-cancer effect by repeated measurement of tumor size to see if tumors have shrunk since the beginning of the trial.

Phase III studies usually compare a new treatment that appeared to have an effect in the small Phase II studies with standard (generally accepted) therapy, or compare the combination of the new therapy and standard therapy to standard therapy alone. Phase III trials require larger numbers of patients; some trials enroll hundreds or even thousands of patients. Patients are usually randomized (assigned by chance) to the treatments being studied. The group that receives the standard treatment is called the “control” group. The researchers expect that a certain number of these patients will be helped by the treatment.

Phase IV trials may be conducted after a drug has been approved. Companies often, for example, carry out studies of new drugs in patients with different tumors or with different stages of disease. FDA may also request, and the sponsor may agree to conduct, other post-marketing studies to provide additional data to improve the safe and effective use of the drug.

Patient Access to a Clinical Trial for Cancer Therapy

The access process starts with a drug sponsor seeking to develop a new cancer drug, which is usually a pharmaceutical company or a research scientist at a university or at the National Cancer Institute (NCI) at the National Institutes of Health (NIH). Before clinical testing begins, researchers analyze the drug’s main physical and chemical properties in the laboratory and study its pharmacologic and toxic effects in laboratory animals. These are known as pre-clinical studies. If the laboratory and animal study results show promise, the sponsor submits

an investigational new drug (IND) application for FDA review prior to initiating testing in people.

Once FDA has reviewed the sponsor's IND and allowed it to proceed, it progresses subject to the oversight of the local Institutional Review Board (IRB). An IRB is a panel of scientists and non-scientists that oversees clinical research, and approves the protocol for clinical trials. Experienced clinical investigators give the drug to a small number of cancer patients who have no other available therapy. These phase I studies assess the most common acute adverse effects and examine the amount of drug that patients can take safely without unacceptable side effects. Initial clinical studies also begin to clarify what happens to a drug in the human body, how it is changed (metabolized), how much of it (or a metabolite) gets into the blood and various organs, how long it stays in the body, and how the body gets rid of the drug and its effects.

If Phase I studies do not reveal major problems, such as unacceptable toxicity, the next step is to conduct a clinical study in which the drug is given to patients who have medical conditions that may benefit from the potential cancer drugs. Several different types of cancers are often explored in these Phase II studies. Researchers then assess whether the drug has a favorable effect on the condition.

Testing experimental drugs in people inevitably presents ethical questions. For example, there have been discussions of when it is ethical to give some patients placebos. A general principle, agreed on internationally, is that patients in a study must not be denied known effective treatment that prevents death or serious injury. In cancer trials, patients are never

denied such treatment. Placebos may be used when there is no known effective treatment. In a so-called add-on study, when the new drug is added to standard treatment, it is typical for study participants to get the standard treatment in an unblinded way. Patients are then randomly assigned treatment with the new drug or a placebo in addition to the standard treatment.

FDA recommends that anyone interested in participating in a clinical trial discuss the idea with his or her physician. Doctors are generally aware of investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. Patients can obtain detailed information from a variety of sources, including drug sponsors, FDA (if the information is public), and NIH. In fact, industry-sponsored trials are statutorily required to be listed on www.clinicaltrials.gov.

Clinical trials are carried out at major medical research centers, at NIH, and even in doctors' offices. Although they often involve hospitalized patients, many clinical trials can be conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out often runs newspaper advertisements recruiting potential participants for clinical studies that tell readers where to call or write for further information.

These aspects and other implications of taking part in a clinical trial must be fully explained in advance by the people conducting the trial, and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug or the desire to take part in research that might one day benefit millions is what makes people volunteer for clinical

trials. It should not prevent them, however, from finding out all they can about being a part of the process. They must also understand that new treatments, although promising, may prove ineffective or harmful.

Trends in Cancer Drug Development and FDA Approvals

Since FDA last testified on this issue before this Committee in June 2000, a number of important cancer drugs have been approved and are helping cancer patients. Of particular interest in recent years are a number of drugs that are not the so-called cytotoxic agents (drugs that are broadly toxic to rapidly growing cells), but are more targeted to specific parts of cancer cells. A few of these drugs that have been approved and are successful for thousands of cancer patients include: Velcade for the treatment of multiple myeloma; Iressa for non-small cell lung cancer; Erbitux for refractory EFG-receptor expressing metastatic colon cancer; Avastin for initial treatment of metastatic colon cancer; Campath for treatment of refractory chronic lymphocytic leukemia; Bexxar and Zevalin for treatment of non-Hodgkin's lymphomas and Gleevec for pediatric and adult chronic myeloid leukemia (CML), and gastrointestinal stromal tumors (GIST).

Expediting Approval of Cancer Therapies

The Food and Drug Administration Modernization Act (FDAMA), enacted November 21, 1997, amended the FD&C Act relating to the regulation of food, drugs, devices, and biological products. With the passage of FDAMA, Congress enhanced FDA's mission in ways that recognized that the Agency would be operating in a 21st century characterized by increasing technological, trade, and public health complexities. Among other things, FDAMA codified

many of FDA's initiatives and existing programs designed to expedite drug development and expand access to unapproved therapies. All of these programs have been instrumental in shortening the time to marketing approval for cancer drugs and biologics. FDA programs codified in FDAMA include:

- **Expediting Approval of Cancer Drugs** – The FDA has shown a long-standing commitment to the prompt consideration and, when appropriate, early approval of new therapies for cancer patients. In 1996, the Agency launched its “Reinventing the Regulation of Cancer Drugs” initiative with the goal of accelerating the approval of and expanding patient access to cancer drugs. This program described how FDA’s Accelerated Approval Rule or Subpart H Approval (21 CFR 314.510) would be used to approve cancer drugs earlier in their development and for expanded access programs (the treatment IND) to be used to make promising drugs broadly available prior to marketing.
 - **Accelerated Approval or Subpart H Approval** - Under the Accelerated Approval Rule subsequently incorporated into the Fast Track provision of FDAMA (section 112), FDA can approve treatments for serious or life-threatening conditions that demonstrate the potential to address unmet medical needs on the basis of a “surrogate endpoint” that is “reasonably likely” to predict clinical benefit. A surrogate endpoint is a measure of drug effect (e.g., tumor shrinkage) that does not by itself show a patient benefit, such as decreased pain or longer survival, but is thought likely to lead to such a benefit. Some surrogate endpoints are well established (blood pressure, for example) and are a routine basis for approval. Other surrogate endpoints are not as certain, and these may now be used under our Accelerated Approval authority. The reinvention program specifically declared that FDA would rely on tumor shrinkage in refractory cancer as a basis for approval, and we have regularly done so. Since 1996, four out of nine biological products were approved under accelerated approval, and many new drug approvals have been based on this study endpoint, allowing for earlier marketing than would have been possible had FDA waited for a documented effect on such an endpoint or survival. Under accelerated approval, the manufacturer commits to study the drug’s actual clinical benefit after marketing.
 - **Expanded access**- Expanded access mechanisms are designed to make promising products available as early in the drug evaluation process as possible. Several other FDA procedures encourage or speed cancer drug development. Prior to drug approval, single patient and expanded access programs provided promising cancer drugs to patients with advanced cancer. Programs for patient use prior to drug approval include single-patient protocols, single-patient exemptions, protocols for treatment, and treatment INDs. Because of the large number of patients with metastatic lung cancer and limited therapeutic options available to patients with

progressive disease, over 20,000 patients received the drug, Iressa, prior to its approval through a protocol designed to provide patient access to this promising drug.

- **Priority Review**-When marketing applications are submitted they are designated as priority (P) or standard (S). Priority New Drug Applications (NDAs) and effectiveness supplements are those that could have important therapeutic impacts. A priority designation is intended to direct overall attention and resources to the evaluation of applications for products that have the potential for providing significant therapeutic advances. Specifically, FDA's goal is to review a priority NDA within 6 months rather than the standard review time of 10 months. Since 1996, 13 biologics (9 BLAs and 4 supplements) and 55 drugs (27 NDAs and 28 supplements) for cancer therapies have received priority review and approval.
- **Fast Track** refers to a process for interacting with FDA during drug development. The fast track programs are designed to facilitate the development of and expedite the review of new drugs and biologics to treat serious or life-threatening conditions that demonstrate the potential to address unmet medical needs. "Rolling Review" is allowed for certain applications that receive fast-track status. To provide clear information to industry regarding participation in the fast track process, FDA issued a guidance document on this provision in September 1998.

Fast-track designation for a clinical development program can occur at any time of the development process. It is initiated by the sponsor's request for designation and can be granted for any development program (as projected by the sponsor) that is intended to demonstrate that its drug/biologic will affect a serious or life-threatening disease or condition. This may be an improvement over existing therapy or treatment where no alternative therapy exists.

It is important to note that FDAMA did not alter FDA's effectiveness standard, except by giving explicit authority to the Agency to rely on data from a single, adequate and well-controlled clinical investigation and confirmatory evidence as support for approval in certain cases. Even for drugs intended for serious and fatal illnesses, there must be substantial evidence that the drug will have the effect it purports to have. As noted, however, the law

recognizes that the nature of the effect that needs to be demonstrated might vary depending on the urgency and clinical need.

Expanding Access to Cancer Therapies Approved in Other Countries

Part of the reinvention effort was to see whether there were useful drugs available in other countries, but not in the U.S. In 1996, FDA sent a letter to the regulatory authorities of 24 countries requesting a list of all cancer or cancer-related therapies approved in their country over the last 10 years. Detailed responses were received from 15 countries. In 1996, forty-four drug products not marketed in the U.S., but marketed in one or more of these countries, were identified. In 1998, the Agency completed its evaluation of the drugs identified as having been approved in foreign countries. Some of them were later approved in the U.S.; some are under review. The Agency concluded, however, that there did not appear to be significant differences in the spectrum of drug products available for the treatment of cancer in the U.S. and in foreign countries. There are no products that appear to potentially provide a significant benefit in cancer treatment that cannot be accessed by U.S. patients, either in the marketplace or through an established IND mechanism.

FDA is Working with Other Organizations to Increase Participation of Cancer Patients in Clinical Trials

Scientific experts from CDER routinely meet with representatives of scientific professional societies including the American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR) as well as their counterparts from the NCI's extramural program. CDER and FDA's Center for Biologics Evaluation and Research (CBER) have developed workshops in conjunction with ASCO, AACR, and NCI, with

participation from academia, industry, and patient advocacy groups. As part of these workshops, the group has re-assessed clinical endpoints for approval of cancer therapeutics. Resulting from what was learned at the workshops, FDA issued formal guidance, as sought by its FDA's Oncologic Drugs Advisory Committee. Other similar workshops have been held over the last few years to address concerns regarding endpoint issues, including endpoints in lung cancer and in colon cancer. Further discussion of endpoints was addressed at subsequent advisory committee meetings. CDER and CBER experts are developing guidance documents on these topics.

FDA meets monthly with the NCI Cancer Therapy Evaluation Program (CTEP) to discuss issues in oncology drug development, including patient access, protocol design, and novel agents under development. Scientists from CDER and CBER's Oncology Divisions attend weekly protocol meetings conducted by NCI for review of NCI-funded trials and proposals for new trials. In addition, FDA sponsors visiting fellowships for medical oncology fellows from cancer centers and major universities.

FDA Office of Special Health Issues (OSHI)

FDA staff is aware of the frustrations that patients with life-threatening illnesses and their families experience when trying to obtain information about potentially helpful therapies, especially when there is no treatment for their disease. In addition to staff within FDA's medical product centers that routinely provide assistance and information to consumers, FDA, in 1988, created the Office of Special Health Issues with trained staff to work with patients with life-threatening diseases. The skilled staff of FDA's Office of Special Health Issues

works with patients with serious or life-threatening diseases such as AIDS, cancer, Parkinson's disease, or Alzheimer's disease, to name a few.

Patients usually call to obtain information about unapproved treatments currently being researched. Once our staff explains that FDA cannot disclose certain confidential information about drugs or devices that are not yet approved, we direct callers to listings of clinical trials where they can locate a trial for which they might be eligible.

We are able to talk with patients about any treatment that appears in a public access database, such as the *ClinicalTrials.gov* database operated by the National Library of Medicine or the National Cancer Institute's database at <http://cancertrials.nci.nih.gov>. Our staff is working actively with the National Library of Medicine and the pharmaceutical industry to include more clinical trials in the *ClinicalTrials.gov* database. If a patient does not have a computer, a patient can access the NCI's clinical trials by calling 1-800-4-CANCER. An information specialist will search the database and send the trials information to the patient within 3 days.

Our goals in serving patients with life-threatening diseases and their family members are straightforward:

- Promptness (returning patients' and family members' calls within 24 hours);
- Accessibility (listening to the caller's concerns and giving the caller as much time as he or she needs);
- Education (about the drug approval process and his or her options); and
- Assistance (providing additional information to the patient or family member that may be helpful, e.g. other sources of information).

We estimate that we receive approximately 1,000 inquiries (phone and e-mail) from patients and family members annually.

During the past 16 years, FDA has made a substantial commitment to assist patients and consumers who wish to become more involved with the drug approval process. We have initiated two programs to integrate patient advocates into our regulatory process: the Patient Representative Program and the Cancer Drug Development Patient Consultant Program. The Patient Representative Program recruits and trains advocates to serve as advisors on FDA's advisory committees considering drugs to treat life-threatening diseases. Since the inception of the Patient Representative Program, over 100 patient representatives have participated in more than 70 advisory committee or panel meetings. Examples of disease areas that have had patient representatives are: AIDS, cancer, diabetes, Parkinson's, temporomandibular joint disorder, irritable bowel syndrome, congestive heart disease, hepatitis B and C, polio, sickle cell disease and lupus, and most recently, major depressive disorder. Patient representatives are appointed as special government employees and must adhere to conflict of interest and confidentiality regulations. We select the patient representatives from their disease advocacy communities, base the selection on specific entry criteria, and when selected, provide them training in preparation for participating in advisory committee meetings.

The Cancer Drug Development Patient Consultant Program involves patient advocates earlier in the drug development process. Cancer patient advocates serve as patient consultants in the pre-approval, clinical trial phase of cancer drug development. The patient consultant participates in FDA and drug sponsor meetings and provides advice to FDA and to the drug

sponsors on topics such as clinical trial design, endpoint determination, expanded access protocol development, and clinical trial patient recruitment strategies.

FDA's OSHI's staff is an access point for the organized patient advocacy community. Many patient advocacy organizations, in addition to providing valuable information to patients, are focused on understanding the specifics of drug approval such as drug labeling.

OSHI staff listens carefully to the patient advocacy community and encourages them to stay involved with FDA's regulatory and policy-making process. We maintain a mailing list of patient advocacy groups who represent the interests of patients with a variety of life-threatening diseases. We routinely notify them about FDA advisory committee meetings, open public hearings or seminars on research or policy and drug approvals, and other FDA issues of interest to patient advocates. Sometimes these small patient advocacy organizations are uncertain about how to approach FDA. The staff wants to be sure that uncertainty and inexperience with drug regulation does not prevent the advocate's voices from being heard. FDA staff believes that the thoughts and concerns of the patient advocacy community are valuable and must be integral to our decision-making process.

The NCI/FDA Interagency Oncology Task Force (IOTF)

The Interagency Oncology Task Force (IOTF) was formed early in 2003 by Dr. Andrew von Eschenbach, Director of the National Cancer Institute, and Dr. Mark McClellan, then Commissioner of Food and Drugs. The formation of the IOTF was an important strategic step toward achieving FDA's goal of increasing the availability and use of safe and effective

treatments for cancer, and NCI's challenge goal of eliminating suffering and death from cancer by 2015. The purpose of the IOTF is to leverage the expertise and capabilities of both agencies for the expressed purpose of streamlining and accelerating the overall development of diagnostic, preventive and therapeutic interventions for cancer.

Since its formation, the members of IOTF have collaboratively undertaken an analysis of the overall development and review process for new oncology drugs and devices and identified several specific initiatives that are directed toward optimizing drug and device development. NCI is working to specifically gather and synthesize the scientific support needed by FDA to address specific regulatory issues. FDA is working cooperatively with NCI to address important scientific issues including:

- Significantly increasing the numbers of physicians and scientists who are expert in clinical research, the clinical approval process and the translation of laboratory science into new products for cancer through high quality training,
- Developing markers of clinical benefit using imaging in oncology drug development, collaborative development of the scientific data needed to establish improved surrogate endpoints for cancer clinical trials, and the potential utilization of advanced technologies,
- Utilizing bio-informatics technology to expand the use of an electronic form of the IND application,
- Establishing an FDA-NCI subgroup to address questions from NCI-supported investigators during any phase of the regulatory review process,
- Enhancing scientifically driven review of the pre-clinical requirements for IND filings; and
- Developing the scientific base for consistent review of cancer prevention agents.

The IOTF is meeting regularly and actively addressing issues that can ultimately speed the development of new advanced interventions for cancer. The IOTF subcommittees are currently developing resource materials that will assist investigators in preparing the data needed for FDA's regulatory process. FDA has already responded with guidance documents (such as a recent guidance on pharmacogenomics) and process changes.

FDA's Critical Path Initiative

On March 16, 2004, FDA issued a report entitled, "Advancing America's Health; Advancing Medical Breakthroughs." This "Critical Path" paper calls for academic researchers, product developers, and patient groups to work with FDA to help identify opportunities to modernize tools for speeding approvable, innovative products to market to improve public health. The report provides FDA's analysis of the current pipeline problem -- the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients, and suggestions for addressing this problem.

Today's revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, affordable, and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased. In contrast, the costs of product development have soared over the last decade.

Because of rising costs, innovators often concentrate their efforts on products with potentially high market return. Emerging contenders for resources include the development of products targeted for important public health needs (e.g., counter terrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging. In fact, with rising health care costs, there is now concern about how the nation can continue to pay even for existing therapies. If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health.

The problem, in FDA's view, is that the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process. For medical technology, performance is measured in terms of product safety and effectiveness. Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's treatment candidates. As a result, the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive

failures. Finally, the path to market, even for successful candidates, is long, costly, and inefficient, due in large part to the current reliance on suboptimal assessment methods.

A new product development toolkit -- containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques -- is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product. Superior product development science is needed to address these challenges -- to ensure that basic discoveries turn into new and better medical treatments. More efforts need to be directed at creating better tools for developing medical technologies. And we need a knowledge base built not just on ideas from biomedical research, but also on reliable insights into the pathway to patients.

FDA is planning an initiative that will identify and prioritize (1) the most pressing development problems and (2) the areas that provide the greatest opportunities for rapid improvement and public health benefits. This will be done for all three dimensions along the critical path -- safety assessment, evaluation of medical utility, and product industrialization. It is critical that we enlist all relevant stakeholders in this effort. We will work together to identify the most important challenges by creating a Critical Path Opportunity List. Concurrently, FDA will refocus its internal efforts to ensure that we are working on the most important problems and intensify our support of key projects.

Through scientific research focused on these challenges, we can improve the process for getting new and better treatments to patients. Directing research not only to new medical breakthroughs, but also to breakthrough tools for developing new treatments, is an essential step in providing patients with more timely, affordable, and predictable access to new therapies. We are confident that, with effective collaboration between government, academia, and the private sector, these goals can be achieved.

Conclusion

FDA is working with NCI, industry, academia, patient and other organizations to ensure that cancer patients receive safe and effective drugs. FDA is also working hard to improve patient access to promising cancer treatments without compromising patient safety. Furthermore, we are working to ensure that patients have timely and important information about available cancer drugs. Our goal is to improve upon a system that supports cancer patients, and all other patients seeking access to new drugs and treatments for their disease.

Thank you for the opportunity to testify. I will be happy to answer any questions the Committee might have.