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White House Announces FDA Initiatives To Accelerate Cancer Drug Approval

One day after a bill mandating FDA reform cleared a Senate committee, the White House and the agency announced a series of reform initiatives that may accelerate approval of cancer drugs.

In the most significant of the four initiatives announced at the White House March 29, Administration officials said FDA would accept data on partial responses as evidence of the efficacy of new cancer drugs.

In recent years, FDA demanded that sponsors demonstrate a drug extends survival, produces complete responses or enhances the quality of life. However, according to several observers, the agency has been

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In Brief

Commerce Dept. Opens Radiation Standards Facility For Mammography Calibration

US DEPARTMENT OF COMMERCE has opened a radiation standard and instrument calibration facility at its National Institute of Standards and Technology in Gaithersburg, MD. The facility will allow the operators and inspectors of mammography centers to trace the accuracy of x-ray exposure measurements to the primary mammography x-ray standards at NIST. The facility was established to assist the Food and Drug Administration in implementing the Mammography Quality Standards Act of 1992, which requires certification and inspection of all US mammography clinics. The instruments used by FDA inspectors to measure the x-ray exposure will be calibrated using the NIST reference x-rays. The facility can be contacted at tel: 301/975-2014. . . . **UNIVERSITY OF ALABAMA** at Birmingham Comprehensive Cancer Center has become the 15th center to join the National Comprehensive Centers Network. . . . **CITY OF HOPE** National Medical Center has received a two-year, $295,000 grant from the National Library of Medicine to design a campus-wide integrated information system. The grant provides start-up funds for development of a data repository. . . . **LA JOLLA** Cancer Research Foundation was renamed The Burnham Institute recently in recognition of supporters Malin and Roberta Burnham of San Diego, CA. . . . **ONCOLINK**, the University of Pennsylvania Cancer Center's on-line resource on the Internet, has selected the International Myeloma Foundation and NCI's Physician's Data Query as the first recipients of its Editor's Choice Awards for excellence in on-line cancer information dissemination. OncoLink's address is http://www.oncolink.upenn.edu.

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FDA Changes Not Enough, Advocates, Oncologists Say

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inconsistent in judging the significance of partial responses.

In other initiatives announced last week, FDA said it would expand patient access to drugs approved in other countries, include cancer patients on FDA advisory committees, and inform investigators that they do not need to file Investigational New Drug applications to conduct certain types of studies of approved drugs.

The changes do not address two issues viewed as central by oncologists and many patient groups: accelerating the approval process for Supplemental New Drug Applications and allowing drug companies to distribute peer reviewed materials on off-label uses of cancer drugs.

"These steps will speed cancer drugs to patients who need them, when they need them," Clinton said as he announced the initiatives. "They will help save lives. They will do this by cutting red tape."

Vice President Al Gore said the policy changes were part of the Administration's "reinventing government" effort begun three years ago.

"One by one, agencies are restoring common sense to regulation," Gore said. "It is because President Clinton instructed people working for him to make government work better and cost less and be more efficient, get rid of the nonsense and replace it with common sense."

Oncology professional societies and cancer patient advocates welcomed the initiatives, but urged the Administration to support legislative reform of FDA.

"While we applaud the Administration for proposing new anticancer initiatives, these initial steps must be accompanied by reasonable and sound legislative reform of the FDA," said John Glick, president of the American Society of Clinical Oncology.

Just the day before the White House announcement, the Senate Labor and Human Resources Committee passed the FDA reform legislation introduced by Sen. Nancy Kassebaum (R-KS). The Administration opposes the legislation (**The Cancer Letter**, March 1).

The committee approved the bill on a 12 to 4 vote. The bill sets rigid deadlines for FDA action on applications and requires FDA to establish a process for approval of SNDAs. However, the bill no longer contains a provision on distribution of information on off-label indications for cancer drugs.

The sponsors of the provision, Sens. Connie Mack (R-FL) and Bill Frist (R-TN) are expected to reintroduce the measure on the Senate floor, sources said.

High Profile Treatment

The announcement was given a high-glitz treatment:

President Clinton met with cancer survivors, signed an executive order declaring April "Cancer Control Month," and invited cancer patients, oncologists, government officials and the media to the East Room.

In speeches, Administration officials evoked the 1992 Clinton-Gore election theme of reforming government using "common sense" while protecting the health and welfare of the people.

"At a time when there are too many reckless ideas floating around Washington, this President, this Vice President, this Administration, has made a profound commitment to reform government, so that we can replace the heartaches with hope for millions of families, so we can help make every cancer victim a cancer survivor, and keep a fundamental promise to the American people: You will always have access to the safest, most effective drugs in the world," said

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HHS Secretary Donna Shalala.

FDA Commissioner David Kessler said the initiatives were developed by agency officials based on scientific considerations, not political events.

"The science dictated this initiative," Kessler said. "We now have the scientific evidence that demonstrates that we in fact can approve drugs on the basis of partial responses, and that's a responsible scientific thing to do."

The accelerated approval process for cancer drugs would go into effect immediately, Kessler said. "I believe you will see new agents emerging under this new regulatory framework within months."

Taxotere, topotecan, and CPT-11 are three cancer drugs that "could be candidates" under the accelerated approval, Kessler said. Taxotere was recommended for approval by the Oncologic Drugs Advisory Committee last October, but is still awaiting market clearance.

"Long Overdue" Changes

In interviews, several observers said no new scientific evidence has emerged on the correlation of tumor shrinkage with clinical benefit.

Accepting partial response data is, unquestionably the right thing to do, said Bruce Ross, formerly an executive with Bristol-Myers Squibb Co. However, it would have been no less right twenty years ago.

"Agreeing to use response rates as a criterion for approval rather than survival data takes FDA back to 1977," said Ross, CEO of the National Comprehensive Cancer Network. "I guess that's what's meant by 'reinventing government.'

"It's a positive change that is long overdue," Ross said to **The Cancer Letter**.

Before 1977, FDA used tumor shrinkage as the basis for cancer drug approvals. However, starting in 1977 and continuing throughout the 1980s, FDA officials said tumor response was not sufficient evidence for demonstrating that a drug improved a patient's quality of life.

The 1977 policy change was based on a decision by the Oncologic Drugs Advisory Committee to recommend against approval of methyl CCNU as a single agent for colorectal cancer. Studies had demonstrated that the drug shrank tumors, but did not produce a survival benefit. Committee members said other drugs as effective and less toxic were available (**The Cancer Letter**, Jan. 21, 1977).

Since the mid-1980s, there has been no lack of pressure on FDA to soften its stance on tumor shrinkage.

In 1986, FDA did not take its committee's advice to approve the drug mitoxantrone for metastatic breast cancer. ODAC recommended approval on the basis that even though the drug did not produce a survival benefit better than the standard therapy, doxorubicin, it was better tolerated.

NCI officials, including Vincent DeVita, then Institute director, charged that FDA's insistence on a survival benefit was impeding cancer drug development (**The Cancer Letter**, Oct. 9, 1987).

In an editorial in Cancer Treatment Reports in 1987, Robert Wittes, then director of the NCI Cancer Therapy Evaluation Program, outlined the Institute's position that a significant complete response rate was a "valid surrogate for survival in cancer treatment."

Thus, cancer drug approvals could be based on phase II studies that demonstrated tumor shrinkage and acceptable toxicity. "Positive phase II studies are generally what convince oncologists of the usefulness of a new agent, long before phase II comparative trials are completed," wrote Wittes, now director of the NCI Division of Cancer Treatment, Diagnosis and Centers.

In 1988, spurred by AIDS activists, FDA adopted new regulations to make promising therapies available for patients with life-threatening diseases. The regulations permitted FDA to approve drugs on the basis of a medical risk-benefit analysis.

In 1990, a committee chaired by Louis Lasagna, a Tufts University professor, recommended that FDA base cancer drug approvals on the results of phase II studies that demonstrate tumor regression. "Survival is in general an impractical and unethical endpoint for cancer drugs," the committee's report said.

New Phone, Address For The Cancer Letter

The Cancer Letter Inc. is moving to a new location in Washington, DC.

The old office will be closed on April 5. The Cancer Letter will reopen at the new location on April 8.

The new mailing address is: PO Box 9905, Washington, DC 20016.

The new telephone number is 202/362-1809. The current fax number will remain operational until the fax new number is determined.

Kessler, confirmed as FDA commissioner in 1990, praised the intent of the report but did not commit to enacting its recommendations.

In recent years, FDA has approved several cancer drugs, including Taxol (Bristol-Myers Squibb), based on tumor response data from phase II studies.

"This is not revolutionary," said Alan Bennett, a partner in the Washington law firm of Fox, Bennett and Turner.

"This is either a return to an older FDA position that they had up until the late 1970s regarding the use of surrogate endpoints, or it means they will do what they always said they would do, which is make accelerated approval available for all serious and life-threatening disease," Bennett said to **The Cancer Letter**.

Michael Friedman, FDA deputy commissioner for operations, said the initiative clarified the agency's requirements for approval of cancer drugs under the accelerated approval program.

"I am not sure that there has been a clear articulation of the value of partial responses in granting approval of cancer products," Friedman said to **The Cancer Letter**. "There is a real advantage in utilizing partial responses as a surrogate marker.

"Complete responses have been used as a surrogate endpoint for a long time, but partial responses could save a substantial amount of time," Friedman said.

The initiative may make it easier for companies to file supplemental New Drug Applications for secondary indications, Friedman said.

Patty Delaney, associate director of the FDA Cancer Liaison Program, said the initiative to include cancer patients on advisory committees formalizes the program's efforts over the past year to invite "ad hoc" patient representatives to committee meetings.

"The important message is that FDA believes by this initiative that the patient's perspective will add to the body of the information about the drug for which approval is being sought," Delaney said to **The Cancer Letter**. "What this person brings is common sense, a patient perspective. I think it would do a lot to bridge the chasm between patients and scientists."

The patient representative will be allowed to vote, Delaney said.

The selection process will be put into place over the next year. "Our goal is to have a neutral third party make the patient selections, and this could take the form of a consortium of cancer organizations, but a final decision has not been made," Delaney said.

Beverly Zakarian, an ovarian cancer survivor and founder of CAN ACT, has been selected as the ad hoc patient representative for the next ODAC meeting, scheduled for April 19. ODAC will consider the NDA for topotecan as a treatment for ovarian cancer.

ODAC also includes a consumer representative, a position currently held by Carolyn Beaman, a science teacher, breast cancer survivor and president of Sisters Breast Cancer Network, of Lake Jackson, TX.

Reaction from Patients, Oncologists

"The President's announcement was a perfect example of political opportunity that benefits people with cancer," said Ellen Stovall, executive director of the National Coalition for Cancer Survivorship. "But the real substance of what was discussed has been in the works for a long time. The science has been there for a while, and maybe the pressure finally came from the community to make the FDA respond."

Stovall said she was disappointed that FDA has not addressed the issue of distribution of information about off-label uses of cancer drugs. "We will continue to press for legislative relief on this issue," she said. "The reason we want a legislative solution is that we don't want to have to wait for another election year to get the reforms that people with cancer need now."

Advocacy groups have tried to work with FDA to enact reforms, but have not met with success, Stovall said. "There hasn't been the commitment inside the FDA to discuss these issues," she said. "It's too easy for change to happen too slowly."

For the past two years, the agency has been without a permanent director for the Division of Oncology since Gregory Burke left for a position in the pharmaceutical industry, Stovall noted. Robert DeLap is the acting director.

"We need a permanent director in place, someone we can go to who can speak to us with the full authority of the agency," Stovall said.

ASCO President Glick said FDA needs to establish a faster process for review and approval of Supplemental NDAs, based on peer reviewed literature.

"Until that mechanism is put into effect, we've got a gap," Glick said. "There is a lot of important information in the peer reviewed literature that is not

accessed by physicians, and companies are restricted in disseminating that information.

"FDA reform should include lifting restrictions on the dissemination of peer-reviewed literature and other reliable information about new uses of approved products," Glick said.

Kassebaum was "pleased" with the Administration's announcement, but thinks further reform is necessary, said Michael Horak, her spokesman. "It illustrates the key points she has been making: FDA has the capacity to review and approve drugs in a much more rapid manner than it is doing, while ensuring the safety and efficacy of those drugs," Horak said.

The Administration's action most likely was in response to the bill, Horak said. "You keep hearing the Administration saying we can't do this, but then they made the announcement they made."

Eugene Schonfeld, president of the National Kidney Cancer Association, said he was happy to see cancer become an election-year issue.

"There's nothing like a Presidential election to get political juices flowing," Schonfeld said. "What is most gratifying to me as a cancer patient is that the President has made 'cancer' a topic in this year's Presidential election.

"But we still have a lot of work to do on FDA issues."

The FDA Initiatives

FDA described the four initiatives in a 12-page document, "Reinventing the Regulation of Cancer Drugs." The excerpted text of the document follows:

Accelerated Approval:

"FDA will substantially expand the use of the accelerated approval process for cancer treatments, based upon verified and recognized demonstration of objective tumor shrinkage. For approval, the potential effectiveness of the treatment should outweigh its toxicities. FDA will also apply the accelerated approval provisions to certain products intended to remove a serious or life-threatening toxicity of cancer treatment.

"For products approved on the basis of tumor shrinkage, post-approval studies will usually be required to further define the utility of the new agent for the approved and/or other indications, either alone or in combination with other agents."

The agency "encourages the submission of supplemental applications for secondary indications and believes that this initiative will significantly expedite the time to marketing approval."

Expanded Access:

"Whenever a cancer therapy for patients who are not curable or well-treated by currently available therapies is approved by a recognized foreign regulatory authority, FDA intends to contact the US sponsor and encourage the submission of an expanded access protocol, regardless of the length of time that the product has been studied in the US.

"The expanded access protocol will be directed at the same general type of patient condition and similar dosage and schedule as formed the basis for the foreign approval. An English-language version of the relevant data submitted to the foreign regulatory authority will be accepted as providing the information needed to consider the expanded access protocol application. If these data are adequate, FDA will permit use of the therapy for appropriate patients under the expanded access protocol...

"To ensure that this process does not become a substitute for obtaining full marketing approval, the sponsor of the product will be required to demonstrate that it is pursuing marketing approval—accelerated or otherwise—with due diligence. FDA will work with the sponsor to develop an expanded access protocol that does not interfere with the enrollment of patients in the studies that will support approval."

Patient Representation:

"It has been FDA's experience that well-informed and motivated representatives of the patient's perspective provide a valuable contribution to the decision making associated with the review of new cancer therapies. FDA has therefore concluded that an ad hoc patient representative with experience in the specific malignancy for which a therapeutic product is under consideration should be included in the advisory committee deliberations concerning that product. This individual will be screened in the same manner as other full members. In order to properly develop a system for selection and service of patient representatives for all future advisory committee meetings on cancer therapies, the agency has enlisted the assistance of an external consultant with expertise in this area.

"This proposal will make more uniform FDA's policy of including patient perspectives on new cancer treatments and responds to public interest in increased participation in the advisory committee process. In addition, the proposal is responsive to a

recommendation of the Institute of Medicine's 1992 Report on FDA Advisory Committees, 'that the concept of consumer be expanded to include patients and patient-oriented organizations.'

The agency plans to publish a notice in the Federal Register to invite nominations for candidates.

Clarification of Policy on INDs:

To reduce the time investigators spend filing unnecessary INDs, FDA will clarify its policy on when an IND is required, the agency said. FDA will not accept an IND for the study of an approved drug in the following cases:

—The study is not intended to support approval of a new indication or significant change in product labeling or advertising.

—The study does not involve a route or administration or dosage level or use in a patient population or other factor that significantly increases the risks associated with use of the product.

—The study meets the requirements for institutional review and informed consent, and does not commercialize the investigational product."

Cancer Information Service Marks 20th Anniversary

NCI's Cancer Information Service marked its 20th anniversary recently by recognizing 10 "outstanding partners in cancer communications."

The CIS was begun in 1976 to fulfill a mandate of the National Cancer Act of 1971 to interpret and disseminate information on cancer prevention, detection and treatment to the public. The 19 offices of the CIS respond to about 600,000 phone calls each year to the toll-free number, 1-800-4-CANCER (1-800-422-6237).

Through outreach with community groups and other government agencies, CIS delivered cancer prevention, detection and patient education information directly to 19 million people in 1995, NCI said in a statement March 25.

The CIS Partnership Awards were given to organizations and individuals who worked with CIS to bring cancer information to the attention of the public.

The awards were presented to:

—Metropolitan Detroit Community Coalition for Cancer Survivorship, Detroit, MI.

—California 5 a Day For Better Health Campaign, Sacramento, CA.

—Elmer Huerta, Washington Hospital Center, Washington, DC.

—AMC Cancer Research Center, Denver, CO.

—Texas Cancer Council, Austin, TX.

—Wai'anae Cancer Research Project, Wai'anae, HI.

—Centers for Disease Control and Prevention, Breast and Cervical Cancer Early Detection Program, Atlanta, GA.

—German Cancer Information Service, Heidelberg, Germany.

—YWCA of Greater Miami and Dade County Inc./ENCORE Plus, Miami, FL.

—International MultiCultural Partnership, Madison, WI.

NCI Sponsors Year-Round Shannon Award Program

NCI has established a program to issue Shannon Awards (R55) three times per year to supplement the NIH Shannon Award program, currently conducted as a single annual competition in the last quarter of each fiscal year, according to a March 29 announcement by the Institute.

The NCI Shannon Award program will offer expedited funding for eligible applications that otherwise might wait up to nine months for the annual NIH Shannon competition, or for resubmission and review as full competing amended applications. Awardees will gain both immediate funding; and, as has been the case for previous Shannon awards, are likely to have improved chances for obtaining subsequent research project grant (R01) support.

Terms of award will be uniform with other NIH Shannon Awards. R55 awards paid with NCI funds will be issued with the standard provisions of a 24-month single budget period at a maximum of $100,000 total cost, with indirect costs capped at a maximum of $20,000.

Applicants do not submit requests for Shannon Awards. Instead, NCI program staff nominate for award previously reviewed eligible R01, R03, and R29 applications that are beyond the current NCI payline. After each of the three review cycles per year, Shannon Award nominations will be administratively reviewed by NCI according to standard review criteria, then submitted to the NIH Office of Extramural Research for expedited review and concurrence prior to funding.

NCI will use its funds to award R55 nominations that become eligible after each of the first two National Cancer Advisory Board rounds in each fiscal year. Such nominations cannot now be considered in a timely way, given the single annual summer date of the NIH-wide Shannon competition supported from the NIH Director's Discretionary Fund. The third round of the year will be submitted under the auspices of the current NIH-wide Shannon Award program.

If the NIH is not able to hold a Shannon competition in a given year, NCI will extend its own program to all three application review rounds. NCI is committed to offer funding for Shannon awards in numbers substantially higher than have previously been possible. It is anticipated that NCI will be able to commit approximately $3 million to the NCI Shannon Award program in FY96.

NCI's continuation of this program in the future is contingent upon the availability of appropriated funds and applications of sufficient scientific merit.

Inquiries: For questions on this process, nominees may contact the NCI program director indicated on the original summary statement. General policy questions may be directed to: Dr. Marvin Kalt, director, NCI Division of Extramural Activities, 6130 Executive Blvd. Suite 600-MSC 7405, Bethesda, MD 20892-7405, e-mail: kaltm@dea.nci.nih.gov

Fiscal or administrative inquiries may be directed to: Catherine Blount, NCI Grants Administration Branch, 6120 Executive Blvd. Suite 243, Bethesda, MD 20892, tel: 301/496-7800, ext. 262.

RFA Available

RFA CA-96-010

Title: **Mechanisms Of Genomic Instability From The Exposure Of Mammalian Cells To High-LET Ionizing Radiations**

Letter of Intent Receipt Date: April 24

Application Receipt Date: June 14

The NCI Division of Cancer Biology and the Life and Biomedical Sciences and Applications Division of the National Aeronautics and Space Administration invite research project grant (R01) applications from interested investigators for studies of the basic molecular mechanisms of long-term (heritable) genomic instability (GI) that is induced in mammalian (or suitable model eukaryotic) cells in organisms exposed to various forms of high-linear-energy-transfer (high-LET) radiation.

The primary interest of both agencies in this RFA is to define and understand GI from chronic low-dose exposure of mammalian cells to high energy nuclei of high atomic number (referred to as HZE) particles (e.g., iron) and to high-energy protons, which are likely to be major sources of human exposure to high-LET radiation during extended space flight. It is also of interest to delineate the mechanistic basis for GI from chronic low-dose exposure of mammalian cells to low-energy neutrons or alpha particles (a surrogate for radioactive radon daughters) that are important sources of human exposure in environmental and certain occupational settings. In addition, both agencies have a continuing interest in the possible use of molecular changes that may accompany radiation-induced GI as biomarkers of human exposure to high-LET.

This RFA will permit a wide range of research activities, including, but not limited to, the following objectives:

•Analysis of the role of the radiation-induced cell-cycle check points on the expression of GI;

•The identification of DNA-sequences and specific genes that exhibit instability during the expression of GI, the analysis of the mutational changes that such DNA sequences undergo and their underlying generating mechanisms;

•Molecular studies to determine if there is a cytogenetic mechanism(s) to account for both the progressive chromosomal and genetic instability observed in cells expressing radiation-induced GI;

•Analysis of the role of recombination and DNA repair on the expression of radiation-induced GI;

•Studies with preneoplastic cell lines, in vivo (implanted) and in vitro, to determine temporal and molecular relationships of radiation-induced GI to neoplastic transformation of non-immortalized cells;

•The temporal and molecular relationships of radiation-induced GI to the acquisition and expression of a "mutator" phenotype among the progeny of irradiated cells.

It is anticipated that 10 awards will be made with a total set aside not to exceed $2 million for the first year to fund applications in response to this solicitation.

Inquiries:

The RFA may be obtained electronically through the NIH Grant Line (data line 301/402-2221), the NIH GOPHER (gopher.nih.gov), and the NIH Website (http://www.nih.gov), and by mail and e-mail from:

Dr. Richard Pelroy, NCI Division of Cancer Biology, 6130 Executive Blvd. Suite 530-MSC 7391, Rockville, MD 20852-7391, tel: 301/496-9326, fax: 301/496-1224, e-mail: pelroyd@epndce.nci.nih.gov.

Dr. Walter Schimmerling, NASA Space Radiation Health and Radiation Biology Programs, NASA Headquarters/Code UL, 300 E Street SW, Washington, DC 20546-001, tel: 202/358-2205, fax: 202/358-4168, e-mail: wschimmerling@hq.nasa.gov

RFP Available

RFP N01-CP-61015-21

Title: **Biological Specimen Repository for Patients at High Risk for Cancer**

Deadline: Approximately May 17

The Genetic Epidemiology Branch, NCI Division of Epidemiology and Genetics, is recompeting a contract currently performed by Biological Research Faculty & Facility Inc.

This is a 100% small business set-aside, SIC code 8731, size standard of 500 employees. The offeror must provide support services to maintain and operate this repository.

The objective is to establish fibroblast cultures (on 50 to 100 new primary skin biopsy specimens per year), establish epithelioid cultures (on 20 to 50 primary skin or organ biopsies per year), grow for storage and dispersal 100 to 200 established cell lines per year, propagate and store up to 20 tumor lines established elsewhere per year, grow 1/4 to 1 gram of fibroblast cell lines or tumor cells from 50 to 150 cell strains per year, Epstein-Barr Virus transform lymphocytes and expand to 1 gram, 50 to 200 lymphoblastoid lines, and maintain approximately 4,000 existing cell lines.

The contractor shall maintain this repository using the most current laboratory techniques for ensuring the highest viability and cell yield from the cultures and to distribute cell lines to laboratory scientists as requested.

This repository contains over 3,000 skin fibroblast, epithelioid, lymphoblastoid and tumor cell lines contributed by members of the DCEG, outside collaborators and other cell banks. These cell lines are also propagated in bulk for DNA extraction for gene mapping studies.

The contractor shall receive and process specimens on weekends, holidays or in the evening, if field trips or the needs of patients under study so require, supply routine pickup of specimens, have available emergency service, using contract taxicab or commercial messenger service, for 24 hours per day, seven days per week, for pickup at area transportation centers, hospitals, private physicians' offices or private homes.

Pickup activities must be initiated within one hour of being notified and delivered to the laboratory within two or three hours of pickup. For this reason, the contractor's facility should be within one hour's distance from the main NIH campus. In addition, the contractor shall receive and process a large number of specimens at one time (e.g., from 10 individuals or more on one day) when necessary.

The contractor shall provide tissue culture transport media (stable non-CO2 buffered media resistant to pH changes that might be detrimental to biopsy growth).

All cell lines shall be routinely screened for contamination by bacteria, mycoplasma or fungi. Protocols for assessing these exposures shall be spelled out by the contractor. All outside cell lines shall be screened to ensure that they are of human origin and not contaminated with animal or other tumor cells. The contractor must have high quality tissue culture facilities, including laminar flow hoods of the type approved by the NCI.

Tumor cell lines shall be handled in separate facilities and shall be processed in laboratory modules where no animal tissue cell culture work is performed. Specimens shall be alpha-numeric coded. All biospecimens stored in the repository must be entered into the Biospecimen Inventory System, an information system designed to track and control the acquisition, storage, requisition and distribution of biological specimens.

Cell lines established from primary samples shall be viably frozen at the earliest passage where at least 8-10 vials can be stored in vapor phase of liquid nitrogen using appropriate controlled rate freezing techniques. All cell cultures and lines shall be stored under optimum conditions in liquid nitrogen freezers. Freezers shall have a constant central source of liquid nitrogen with emergency back up and automatic filling mechanisms. The contractor shall provide a 24-hour central alarm and sentry system with active surveillance 24 hours per day, year round, with explicit directions on the steps to take in case of emergency. Freezer areas must have fire and smoke alarms.

At present, there are approximately 16,000 vials in storage. A minimum of three vials must be maintained per cell strain, with a maximum of 20 vials per strain. Clearly documented inventory records shall be maintained.

The contractor shall respond to written requests for cell lines from approved investigators. The contractor shall make all arrangements for shipping or delivery of specimens.

It is estimated that a maximum of 500 specimens shall be sent to outside collaborators each year, of which 200 shall require shipment to collaborators outside of the Washington, DC, metropolitan area. A maximum of 500 specimens each year shall be sent to investigators who are not directly collaborating with NCI. A fee of $75 shall be charged to defray handling and shipping costs for requests from investigators not directly collaborating with NCI.

A level of effort of 19,850 total direct productive labor hours, over a period of five years is required. The contractor must have available personnel with qualifications, experience and capabilities to accomplish the above requirements.

Contracting officer: Barbara Shadrick, NCI RCB, CECS, 6120 Executive Blvd. EPS Rm 620, Bethesda, MD 20892-7224, tel: 301/496-8611.