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FDA, NCI Remain At Odds Over Drug Approval Guidelines Despite Reconciliation Discussion

What started out as a seemingly friendly effort to discuss differences between the oncology community and the Food & Drug Administration developed into a brisk and sometimes

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In Brief

NCI To Move From Westwood, Landow, Blair Bldgs; Kinsella Named UW Oncology Chairman

NCI OFFICES in three suburban Maryland buildings will be moved to one new building in Rockville about three miles north of the NIH campus during the first half of next year. More than 1,000 staff members now working in the Westwood and Landow buildings in Bethesda and the Blair building in Silver Spring will be involved in the move. These include staff from the Div. of Cancer Biology & Diagnosis, Div. of Extramural Activities and the Grants Administration Branch in Westwood; Div. of Cancer Etiology and Div. of Cancer Treatment in Landow; and Div. of Cancer Prevention & Control and Research Contracts Branch in Blair. The new building is close to a Metro subway station, has several meeting rooms and was designed to accomodate computer and advanced communication facilities. . . . **TIMOTHY KINSELLA**, professor of human oncology at the Univ. of Wisconsin (Madison), has been named chairman of the Dept. of Human Oncology. **Paul Carbone**, who has been department chairman since 1977 and director of the UW Clinical Cancer Center, will remain in the latter position. Kinsella recently joined UW from NCI, where he was director of radiation oncology training. He will direct the radiation therapy clinic at UW Hospital & Clinics. . . . **GAIL JOHNSTONE** has been appointed director of planning at Roswell Park Memorial Institute. She will head development of a long range strategic plan and a facility master plan and will serve as liaison to various regional, state and federal agencies. She has been director of planning for the city of Buffalo. . . . **GERARD BURROW**, chairman of the Dept. of Medicine at the Univ. of Toronto and physician in chief of Toronto General Hospital, has been appointed vice chancellor for health sciences and dean of the Univ. of California (San Diego) School of Medicine. He will succeed Robert Petersdorf, who left last year to become president of the Assn. of American Medical Colleges. Wayne Akeson, acting dean since Petersdorf's departure, will continue until Burrow's arrival next spring.

Neither Side Budges, But FDA, NCI Agree To Meet Again On Guidelines

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sarcastic confrontation. It ended friendly enough, with agreement on the need for continuing discussions, but neither side indicated much willingness to change its position.

The occasion was the Board of Scientific Counselors of the Div. of Cancer Treatment. The participants included FDA Commissioner Frank Young and NCI Director Vincent DeVita. The issue was FDA's policy regarding requirements for approval anticancer drugs.

That has been an ongoing source of disagreement between the two agencies at least since the early 1970s. The discussions "are more pleasant now" than then, DeVita said, "but they don't solve the problem of getting anticancer drugs to market."

The appearance of Young may be unprecedented. A decade ago, the FDA commissioner insisted on the protocol of rank and would talk only with his administrative equal, the NIH director. Neither was much interested in the problem of speeding approval of anticancer drugs. The NCI director was on the same level as the FDA Bureau of Drugs director. Richard Crout, then head of the bureau, ignored protocol, developed a good rapport with DeVita, then DCT director, and they managed to overcome the immediate problems of the day.

Things aren't so stuffy now, and Young, DeVita and DCT Director Bruce Chabner are all on a first name basis and have met along with other staff members on a number of occasions to discuss their problems.

Young opened the discussion by claiming that during his tenure the approval process has been cut from an average of 25 months to 12, but it "is like turning a battleship in a river."

Young said FDA gives "highest priority" to approval of oncologic drugs and revealed his own personal interest in cancer. His mother died of the disease, and within the last year, he had a superficial melanoma removed. "I was told that there is 94 percent survival with that type of cancer, which I think is wonderful unless I'm in the other six percent." A pathologist, much of his academic career was supported by the American Cancer Society.

Young noted that by December he will have served three and a half years as commissioner, the longest tenure in that job since 1966.

One of the main sources of contention between FDA and NCI has been that FDA sometimes has ignored the advice of its own Oncologic Drugs Advisory Committee. Young addressed that by pointing out that the agency's advisory committees are strictly advisory and that the law places entire responsibility for regulating drugs on the staff and commissioner. "FDA sees a lot more information (in the new drug application submissions) than the advisory committee or what appears in the literature," Young said.

Robert Temple, office director of the FDA Div. of Oncologic & Radiopharmaceutical Drugs, did most of the talking for his agency and received most of the barbs hurled by BSC members and NCI staff.

Temple expressed surprise and even, perhaps, injured feelings over the criticism from NCI.

"We have considered ourselves in the mainstream on these issues," he said. "We've discussed approval criteria with our committee. We've not been told our general approach is at odds with what most people think. NCI staff members attend the committee meetings and we have meetings with industry. I can't recall a single instance in which we were told of any policy differences. . . The idea that a new drug should provide a major benefit and not just tumor regression is not something FDA invented."

He was surprised, therefore, when DeVita wrote a letter obecting to FDA's insistence that survival had to be demonstrated to gain NDA approval. FDA's position was standing in the way of development of effective anticancer drugs, while NCI's position is that other endpoints should be considered, Temple said in quoting DeVita's letter.

"Any impression by the head of the National Cancer Institute that FDA impedes cancer drug development is something we take seriously," Temple said.

Temple said he was also surprised when he read in **The Cancer Letter** (June 26) Chabner's statement at the June meeting of the BSC in which he challenged FDA to openly debate the issues. Chabner's criticism had been brought on by FDA's disregard of the advisory committee's recommendation for approval of mitoxantrone and vindesine. Disapproval was based on failure of the studies to show any survival improvement.

"We do not intend that survival be the

only satisfactory endpoint," Temple said. "We consider any evidence of benefit," but insisted that benefit must outweigh adverse effects.

He cited approval of alpha interferon for treatment of hairy cell leukemia as one example, since impact on survival was not a consideration although benefit was clear. Also, tamoxifen was approved for adjuvant therapy of breast cancer on the basis of delay of recurrence and improvement in quality of life, with no formal presentation on survival improvement.

"These are examples that show there is no stubborn insistence on survival," Temple said.

"One of the drugs Dr. Chabner cited in **The Cancer Letter** as deserving approval is vindesine," Temple continued. "There is not much evidence that it represents a gain over no treatment at all. . . I'm sensitive about vindesine. We are available for discussion over our differences, but we didn't have any. . . We do not often disagree with our advisory committee, only five times in the last 50 votes."

Temple concluded by saying that "the disagreement is not between NCI and FDA but reflects disagreement within the scientific community."

Chabner was the first to respond. "While you said survival is not the only endpoint, you kept returning to it." He pointed out that most patients involved in drug tests used to support NDAs are in advanced stages with limited survival expectations. "You have to look at other things, such as response rate and toxicity. It would provide a real advantage to practicing physicians to have a choice."

Chabner argued that mitoxantrone, while not as effective as adriamycin in survival impact, caused significantly less toxicity. Many patients can't or won't tolerate adriamycin but can take mitoxantrone. Even if survival is reduced five to 10 percent, "the tradeoff is significant. It is better than no treatment (when adriamycin is refused)."

Temple said that new data on mitoxantrone have been submitted, and "although I can't talk about it now, I can't tell you everything I know, you will agree with me in a month or two."

DeVita took the offensive. "In all the examples you offered, you didn't give a single example of a new cancer drug being approved for the treatment of metastatic disease. Interferon for hairy cell leukemia is not an example."

Even if mitoxantrone is not as effective as adriamycin, "a drug half as good as a single agent may be twice as good in combination with something else," DeVita said.

The fact that the FDA advisory committee disagreed with the agency only five out of 50 times did not impress DeVita. "You stack your committee with people who agree with you," he said. But he pointed out that a substantial majority of the committee now disagrees with FDA on the issue of whether relief of symptoms should be considered important enough to secure approval for a drug.

Temple had intimated that industry representatives had not disputed FDA guidelines. DeVita responded that that was because NCI is the only institution sponsoring new drugs which can challenge FDA without being apprehensive about jeopardizing approval of its drugs.

Temple had mentioned cisplatinum as an effective anticancer drug approved through FDA's normal process.

"You should be careful about using that as an example," DeVita said. "You held up approval of cisplatinum long after its effectiveness and impact on survival had been widely known to oncologists."

"I don't want to sound whiney, but if someone thought our stance was wrong, I don't see why someone didn't talk with us about it," Temple said. "The vindesine decision was made two and a half years ago."

Board member Lawrence Einhorn argued that if the advisory committee votes 5-4 in favor of a drug "and FDA agrees, that's okay. But if the vote is 9-0 and FDA goes the other way, the final decision should be approval."

Einhorn said the vote for approving etoposide for treatment of small cell lung cancer was unanimous by the committee or nearly unanimous but approval by FDA was held up for a year, although a significant improval in survival had been shown.

"We take the committee's views seriously, but we don't always agree," Temple said.

Einhorn suggested that since the advisory committee "is a group of experts, if they approve a drug and FDA disagrees, then at the next meeting it should be brought back and if the committee votes again to approve," FDA should be required to approve.

Samuel Broder, director of DCT's Clinical Oncology Program, pointed out that FDA

approved AZT for AIDS patients without first accumulating the extensive data base required for oncologic drugs, but that since then, "an enormous" amount of data has been gathered which "endorses confidence in it." He suggested that earlier approval of cancer drugs would be reinforced by later experience with them.

FDA's policy of requiring proof of equivalent survival from a new drug compared to standard treatment will impede development of new AIDS drugs. Randomized trials now will use AZT as the control, and it could take years to meet FDA's standard of an equal impact on survival.

Robert Wittes, director of DCT's Cancer Therapy Evaluation Program, said that criticism of FDA as being "paternalistic" and impeding clinical research with unnecessary red tape is similar to that sometimes leveled at CTEP. "We attempt to deal with that by getting the community as a whole involved in decisions. That is significantly different than how FDA deals with industry."

Wittes added that "there is a pervasive lack of leadership from FDA. . . My suggestion is for the agency to be out in front."

Stephen Carter, vice president for anticancer research at Bristol-Myers and former deputy director of DCT, said that the impact of FDA's policies leads to lower probability of success in development of new drugs, restricts indications for use of drugs that are approved, requires larger numbers of patients in trials than are necessary, demands prolonged followup and diminishes scientific interest in pivotal studies.

FDA's limit on indications sometimes makes it unfeasable for a company to market a drug, Carter said. Cisplatinum has been approved only for testicular, ovarian and bladder cancer, although its effectiveness has clearly been seen in head and neck cancer, small cell lung cancer, cervical cancer and osteosarcoma. Although physicians may prescribe the drug for those sites, the company can't promote it for those uses and can't include them on the package inserts. "There are significant problems" in proving an impact on survival in those areas.

The story with VP-16 is another example cited by Carter. The drug was approved for testicular cancer in 1982, although the company had asked for small cell lung cancer to be approved as well. "We were told it was not approved because it was not equivalent to vincristine." So further studies were undertaken which, four years later, were accepted, and small cell lung cancer was added to the indications for VP-16. "It took us years of work and lots of money to prove it was a useful drug against small cell lung cancer, when the oncology community knew it was all along."

Martin Abeloff, who has been chairman of the FDA Oncologic Drugs Advisory Committee for more than three years, said that there is a difference in philosophy between FDA and the committee. Survival is not used as the sole criteria, but "clear cut effects on quality of life are seldom demonstrated. . . It is the opinion of the committee that interval to progression and length of response are reasonable surrogates for quality of life. Decrease in toxicity and relief of symptoms are also important criteria. . . We can do a better job of showing relief of symptoms and improvement in quality of life. We're all guilty of not making the effort to measure these things."

"We've never said we would not accept palliative results," Temple said. "We never see them."

"They're buried in the reports, as partial responses," Chabner said.

"I've been struck by the incredible disparity between what you say you are willing to do and how you act," Dan Longo, director of DCT's Biological Response Modifiers Program, said.

Broder asked if FDA would consider the cost of a drug in determining approval. He had in mind the current effort to develop replacements for AZT which might be cheaper. Temple said that would be "very difficult for a regulator to do."

Board member Susan Horwitz asked how many oncologists are involved in reviewing cancer drugs; Temple said there are three.

Board member James Cox asked if there had ever been a conference on the issue of endpoints. DeVita said no public conference has been held, although FDA and NCI have been discussing it. "A public conference involving this Board might be a good idea." Temple said FDA was trying to initiate such a conference, but DeVita said "that ought to be out of the auspices of FDA." Chabner invited FDA to continue discussions with the Board and NCI

Young promised that "within six months I will present our strategy for review for approval, we will determine a process that involves your input, we will determine the best way to provide guidance to the agency--

in no way will I subvert the role of the advisory committee--and we will explore the extent to which we can use the drug ward at the Institute of Medicine.

"This is the first time the FDA commissioner has been invited to this meeting," Young continued. I did not get the support I would have expected from the academic community. I will be back in six months to give you this report."

DeVita thanked Young for coming but added that "the commissioner shouldn't have to come here on this problem." He suggested that the Board take up the suggestion to organize a consensus conference on endpoints to be considered in new drug approval.

Senate Committee Tells NCI To Fund Centers At Full Levels With $118 Mil.

The Senate Appropriations Committee added only $3 million to the recommendations of its Labor-HHS-Education Subcommittee for NCI's 1988 fiscal year budget, still leaving it about $10 million less than approved by the House. But the committee did earmark $118 million for the Cancer Centers Program and directed that cancer center core grants be funded at their full recommended levels.

The committee agreed with the House in not providing any money for construction or renovation of cancer releated facilities, pending completion of a study on research construction needs. But the committee directed that the NCI construction program staff be kept intact so that "expert staff not be lost in the event Congress determines next year that the program will be continued and funded."

The Senate committee total for NCI is $1.527 billion, which includes $93.9 million for AIDS research.

Noting that cancer center core grants were funded at only 85 percent of peer review recommended levels in 1987, the committee said that to address this shortfall, funds are included to pay all core grants at their full recommended levels. "The committee is also aware that there are a number of requests pending for new cancer centers. The committee believes that adequate funds are available for new centers if the directors of NIH and NCI agree new centers are important for programs in good science. The committee has included $118 million for centers."

The committee report urged NCI to provide adequate resources to the Community Clinical Oncology Program but didn't add money for it.

DCPC Board Okays Concepts For New Master Agreement, Recompetitions

Use of the master agreement contract mechanism by NCI is becoming a popular way to support multifaceted projects while reducing the time from identification of an individual task to be performed to award of a contract, or task order as it is called.

The Div. of Cancer Prevention & Control Board of Scientific Counselors gave concept approval to a new program for cancer prevention and control surveillance, to be supported through master agreements, and approved three other master agreement recompetitions (one of which, for preclinical toxicology of chemopreventive agents, was reported last week in **The Cancer Letter**).

The new surveillance program will cost nearly $8 million over five years, DCPC staff estimated.

The additional master agreement recompetitions are for evaluation of chemopreventive agents by in vitro screening assays, and evaluation of chemopreventive agents by in vivo screening assays.

The Board also gave concept approval for production of monographs on the Smoking, Tobacco & Cancer Program, to be supported by a contract; and to noncompetitive continuation of the U.S.-Finland studies of nutrition and cancer and the study on basal cell carcinoma being carried out through an interagency agreement with military hospitals.

Concept statements follow:

Cancer prevention and control surveillance master agreement. New program, five years, estimated total cost $1.15 million first year up to $2.3 million in the final year.

The tracking and evaluation of cancer prevention and control activities in relation to the Year 2000 goals require the division wide ability to perform a variety of surveillance activities quickly and efficiently. The purpose of this concept is to establish a master agreement mechanism under which a variety of surveillance activities would be conducted. The goals of establishing the mechanism is to enable the cancer control information to be obtained with a minimum of delay while maintaining the highest standards for surveys and other data collection.

The purpose of the existing and planned surveillance activities of the Institute is to monitor cancer incidence, mortality and survival; prevalence of cancer risk factors; public behavior toward cancer prevention and early detection; physician adoption and implementation of cancer control regimens; and the programmatic response of institutions and organizations. By timely assessment of these indicators, the delivery and content of programs can be adjusted to provide the public and health care professionals with the necessary information to direct their activities most effectively. It will be especially useful to be able to conduct this monitoring in conjuction with the

data collection activities of the Surveillance, Epidemiology & End Results Program (SEER). This will enable NCI to relate changes in cancer control actions to changes in the incidence, mortality and survival from cancer.

The base of information required to monitor cancer control activities is fairly diverse and will call for collection of information from individuals and organizations. These data collections will need to be planned and performed in conjunction with long term monitoring which will be conducted through a variety of survey and monitoring sources. It is likely that some of these surveys will also involve large scale studies of the general public; however, many of these surveys will be targeted toward the organizational subgroups or target populations most impacted by the preventive initiatives. These groups may include health care providers, health department personnel, business leaders, other organizational leaders, minoritory subpopulations or a variety of similar groups.

The exact nature of these types of surveys cannot be specified at this time but the types of anticipated interventions may include large scale media responses to new information on cancer or cancer prevention, new legislative action affecting large numbers of individuals such as smokefree policies or third party payment for preventive services, or introductions of major new coordinating programs by the major health voluntaries such as the Tobacco Free Young America Project. The proposed mechanism lends itself equally well to other applications such as short term surveillance of a cohort including the opportunity to make comparisons over time by repeating questions of interest to the division for which baseline data is already in existence.

For example, extensive data on smoking prevalence, knowledge, attitudes and behavior will be available from a large national survey of the adult population conducted by the Office of Smoking & Health. Selected aspects of that extensive questionnaire could be repeated to track changes related to specific NCI initiated programs. Also, a large body of cancer control baseline data relating to diet, screening and other topics will be available from the 1987 Health Interview Survey Cancer Prevention Supplement.

The recommended mechanism to enable the institute to respond in a timely manner to emergent cancer control survey needs is the establishment of a core of qualified contractors under a master ordering agreement. Qualified firms will be competitively selected for maaster agreements which entitle them to bid on subsequent RFPs for task orders to perform specific surveys. The technical review of the firms is performed at the outset by the Div. of Extramural Activities contract review committee, which judges the capability of the firms to provide the variety of services required. Selection of a contractor for an individual project is then made competitively from among firms with master agreements which submit technical and business proposals for the particular project. This process can be as short as four to six months compared to the usual 12-18 month concept planning and review cycle.

Production of monographs on smoking, tobacco and cancer program. One five year contract, estimated cost ranges from $450,000 the first year to $490,000 the final year.

The overall goal is to develop a mechanism for the identification, collection, analysis, editing, publication and dissemination of effective smoking and tobacco control strategies, particularly those that appear to have the potential for more immediate application. The monograph format would allow a comprehensive and focused presentation of the knowledge gained from the NCI/STCP projects and the implications of that knowledge for tobacco use control. The monographs would serve four major objectives:

A. Enhance the rapidity and efficiency with which NCI can utilize the STCP research findings on smoking and tobacco use as a means of reducing morbidity and mortality for those cancers associated with tobacco use.

B. Significantly shorten the time between the availability of information emanating from research projects and the publication and wide dissemination of this information.

C. Provide a cohesive and integrated description of individual smoking and tobacco use issues, control strategies, prior research results and new trial results to allow maximal utilization and dissemination of current and evolving scientific knowledge and thereby influence the professional and lay public's understanding of these matters.

D. Provide a mechanism for codification and synthesis of information relevant to the use of those agencies, institutions and individuals in the nation which can affect the formulation of public policy related to smoking and tobacco use.

It is anticipated that monographs will be produced quarterly. The number will vary, depending on the topic selected, availability of information emanating from STCP research projects, and the complexity of the material to be covered. Each monograph will focus on specific aspects of the tobacco control problem. Monographs will focus on a target population (e.g., women, minorities or adolescents), an intervention channel or strategy (e.g., smokeless tobacco) or a specific policy area (e.g., smokefree worksite policies).

Focus of the monographs will largely reflect the emerging data bases of the current STCP grant and contract funded trials which are entering the analysis phase in 1988. The monographs will provide a state of the art review of current tobacco use demographics (targeted to the population or strategy of focus), health risks for the populations of interest, an integration of STCP trial results and other important new literature reviews and data sets, a peer reviewed summary of these data and recommended actions for the ongoing tobacco use control effort and an evaluation of the role of these actions in NCI's plans for the Year 2000. The content of each monograph may include the following:

A. A detailed analysis of smoking/tobacco use trends by the target audience being addressed and relevant cancer mortality trends by cancer site for populations.

B. Review of the relevant published scientific literature on intervention and control measures in the target population.

C. Findings from individual STCP projects along with pooled results and analyses as appropriate.

D. Identification of knowledge gaps in smoking control efforts and possible new directions for future research to reduce cancer mortality.

E. Specific public health action plans addressing the types of activities, individually and collectively required by agencies, institutions and individuals to foster the application of the defined control strategies.

F. The significance of the program actions plans in the overal NCI plan for the Year 2000.

The contractor will require expertise in smoking and health and related tobacco use issues, management of scientific reviews, coordination of outside experts, and preparation of scientific reports. Access to a team of experts for peer review and manuscript development in the broad field of tobacco use and health are required. The organization must include individuals knowledgeable about tobacco use, particu-

larly smoking, and its relationship to chronic diseases, particularly cancer.

The contractor will be familiar with survey research data sets on prevalance of smoking and tobacco use; possess expertise in behavioral and psychological issues related to smoking control, including prevention, cessation and intervention research; and be familiar with cancer morbidity and mortality information and the data sources from which it is derived. Smoking, Tobacco & Cancer Program staff shall provide overall guidance and management of the entire compilation process, coordinating all aspects of production from development of initial outlines, to final publication of each volume.

The contractor, in close coordination with STCP staff, shall be required to perform specific services relating to the scientific and medical content of each monograph, including compliation of all summary and quantitative analysis, coordination of peer reviews, generation of draft and camera copy of manuscripts, graphics and graphics support, statistical support for the analysis of numeric data sets, scientific editing, and the management of the scientific editorial team.

Evaluation of chemopreventive agents by in vitro screening assays. Recompetition of master agreements. Staff anticipated that five to six task orders will be issued annually for studies on specific agents. Estimated annual cost is $900,000. Staff had asked that the master agreements be awarded for five years, but the Board reduced that to three.

The primary objective of this study is the in vitro screening for efficacy of various selected chemopreventive agents in various in vitro transformation systems. The in vitro systems selected are a battery of screening systems including the following:

1. Human cells (so that any activity of the chemopreventive agent that might be specific to human cell substrates can be evaluated.
2. Organ cultures where acceptable systems exist (e.g., mammary organ culture), so that any activity of the chemopreventive agent that might be specific to a particular differentiated organ can be evaluated.
3. Cells of epithelial organs are those primarily used (because of the relevance to the human cancer prevention problem in which most of the cancers are carcinomas having epithelial histogenic origins).
4. In vitro systems that allow screening against the different stages of carcinogenesis (e.g., initiation and promotion).

The emphasis of the activity will be to take the initial leads from the published literature and focus on the most promising chemopreventive agents for testing in the in vitro screening system. Promising data obtained from the in vitro screening assays will be used as one criteria for further testing.

All master agreement holders will be asked to submit a master protocol for in vitro screening studies in at least one relevant screening system in their technical proposals which details all aspects of the study except those determined by the specific chemopreventive agent. A standardized protocol will be developed by DCPC program staff for each screening system and for each chemopreventive agent including the number of experimental groups and controls, statistically valid replicates, number of doses of chemopreventive agents, administration of the carcinogen, standardized test for purity of the agent and preparation of the agent, and solubility in tissue culture media, standardized tests for assay of the agent in tissue culture media, criteria for quality control of the tissue culture procedure. The investigator will develop and submit monthly reports and a final report on the results of the study.

"Having lived with chemotherapy screens for years, I don't expect immediate results from this," Board member John Ultmann said. "The presumption is that all agents will be either on the skin or taken by mouth. That requires absorption, transportation, etc. Don't you believe you are trying to look for scientific bases for observations in man a little too early?"

"That is an exceedingly important question, Board member Edward Bresnick said. "In my view, it is a little early. There should be an analysis in a few years of in vitro screening."

"We need to set up a strict set of criteria based on the experience in the chemotherapy arena," Board member Frank Meyskens said. ""If you don't set up that criteria before you start, you will be looking at things the wrong way. You will have problems making evaluations."

DCPC Director Peter Greenwald said that such criteria "are supposed to be in chemoprevention planning, but they probably could be sharpened."

Meyskens suggested an amendment to add a formal system for criteria in advancing agents from in vitro to in vivo to humans; and Bresnick asked that the master agreements be awarded for three instead of five years. Both were included in the motion to approve.

"I would like to make the point that negative results should not eliminate a compound," Ultmann said. The logic of a substance has to override negative in vitro findings."

Evaluation of chemopreventive agents by in vivo screening assays. Recompetition of master agreements. Staff estimated five to six task orders, with a total cost of $900,000 a year. Reduced from five to three year awards by the Board.

The primary objective of this study is the in vivo screening for efficacy of various selected chemopreventive agents in animal models. The animal models are chosen for their relevance to the human cancer problem including an emphasis on lung, colon and breast cancer. The emphasis of the activity will be to take the initial leads from the published literature, and the results from the chemoprevention in vitro screening program and focus on the most promising chemopreventive agents. The efficacy data obtained in the in vivo screening assays on the selected agents will be expanded by an extended efficacy evaluation of the dose response, bioavailability, spectrum of target sites, and potential toxicity as well as studies of combinations of promising chemopreventive agents.

Board member James Gaylor said that the Board's Prevention Committee had suggesting adding an in vivo screen for metastases. Board Chairman Paul Engstrom said that approval of the concept included the request for a metastases model. Approval was unanimous.

U.S.-Finland studies of nutrition and cancer. This was first approved by the Board in 1983 for five years, with an additional three years if an interim review approved. The Board granted the three additional years and also approved modification permitting an increase in the size of the study population. The total cost, which is testing the effectiveness of beta carotene and/or alpha tocopherol in preventing lung cancer among smokers, is estimated at $12.3 million for the entire eight years.

Isotretinoin-basal cell carcinoma prevention study. This study is evaluating a retinoid, isotretinoin, in preventing basal cell carcinomas in a high risk population. DCPC staff said the performance at the five participating military hospitals has been excellent, but unavoidable delays in patient recruitment require a three year extension, which the Board granted. The extension will cost an estimated $325,000 a year.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda MD 20892. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring MD, but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

NCI-CM-87245-11

Title: Hyperthermia quality assurance program
Deadline: Approximately Dec. 20

The Radiation Research Program of NCI's Div. of Cancer Treatment requires the development of criteria, guidelines, procedures and ancillary equipment for hyperthermia systems which have become or have the potential of becoming commercially available, i.e., have FDA premarket approval.

Ultrasound and interstitial devices in particular need to be addressed. The successful offeror shall also conduct a hyperthermia quality assurance program based on the above and shall conduct on site examinations of the hyperthermia systems and procedures at government supported institutions requesting this service.

The preparation and distribution of educational materials that describe recommended standard procedures for the use of hyperthermia systems is also required.

This is recompetition of work currently being performed by Allegheny-Singer Research Institute. It is expected that a cost reimbursement incrementally funded contract will be award for 36 months beginning June 30, 1988.

Contracting Officer: Frank Leon
RCB Blair Bldg Rm 225
301/427-8737

NCI-CN-85061-33

Title: Phase 1 studies of new chemopreventive agents
Deadline: Dec. 11

The Chemoprevention Branch of NCI's Div. of Cancer Prevention & Control wishes to establish a master agreement contract for the above study. The objective of these studies is to determine the parameters and characteristics of toxicity in humans, the safely delivered dose, and the basic clinical pharmacokinetics of agents emerging from the NCI chemoprevention agent development program so that subsequent phase 3 risk reduction trials can be appropriately designed.

The master agreement holder shall develop and conduct the following studies:

Task 1--phase 1 studies. These shall provide the parameters and characteristics of drug toxicity, the safe delivery dose and a recommended phase 2/3 dose. Phase 1 clinical studies with combinations of agents may be performed if mutually agreed upon by the contractor and the project officer.

Task 2--pharmacokinetic studies. These shall provide the parameters of drug absorption, blood concentration time profiles, distribution and excretion. Using classical and nonclassical modeling, the pharmacokinetic data shall be used to determine probable patterns of distribution, and excretion, compartmentalization and enterohepatic recirculation, and to include identification as well as distribution and excretion of metabolites.

The master agreement shall certify a holder's qualification to compete for both task 1 and 2. For a given agent tested, qualifications to carry out both tasks 1 and 2 must exist, although only task 2 may be required.

It is estimated that investigators and institutions shall be deemed qualified via peer review and thus shall be included in the master agreement. A maximum of 10 task orders (including both tasks 1 and 2), requiring approximately 200 subjects, shall be issued annually for a period of five years for studies on specific agents.

Contracting Officer: Vernon Rainey
RCB Blair Bldg Rm 2A07
301/427-8745

NCI CONTRACT AWARDS

Title: Multidisciplined analysis of chemopreventive agents
Contractor: CCS Associates, $342,859

Title: Evaluation of chemopreventive agents by in vivo screening assays
Contractors (master agreement orders): IIT Research Institute, $359,495, $432,449, and $363,091; Univ. of Nebraska-Eppley Institute, $381,064.

Title: Evaluation of chemopreventive agents by in vitro screening
Contractors (master agreement orders): Northrop Services, $275,420; SRI International, $149,165; IIT Research Institute, $243,824; Northrop Services, $190,878 and $268,475.

Title: Efficacy studies of chemopreventive agents in animal models
Contractors (master agreement orders): IIT Research Institute, $134,595, $147,323, $282,451 and $88,004; American Health Foundation, $413,773; and Univ. of Alabama (Birmingham), $242,146.

Title: Preclinical toxicology of chemopreventive agents
Contractor: International Research & Developlment Corp., $310,221

Title: Epidemiological studies of cancer among atomic bomb survivors
Contractor: National Academy of Sciences, $1,497,614

Title: Baseline survey for community intervention trials for smoking cessation
Contractor: Research Triangle Institute, $967,450

Title: Epidemiologic studies of cancer in China
Contractor: Chinese Academy of Preventive Medicine, $102,690

Title: Prospective interdisciplinary study of infection with human papillomavirus
Contractor: Westat Inc., $996,891

Title: Industrial hygiene and biochemical monitoring of exposures encountered by anatomists and embalmers
Contractor: Azimuth Inc., $173,740

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