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FDA Considering Ways To Improve Process Of Secondary Approvals Of Cancer Drugs

FDA is considering options for streamlining and redefining the process for secondary approvals of new anticancer drugs and updating labels on approved agents, NCI Div. of Cancer Treatment Director Bruce Chabner said last week. NCI began presuring FDA to improve its process for secondary approval when the drug agency earlier this year began a crackdown on pharmaceutical firms' promotion of drugs for indications

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In Brief

Mammography Quality Assurance Act Introduced; Laurence Marton Succeeds Brown At Wisconsin

BREAST CANCER SCREENING Safety Act has been introduced in the Senate by Sens. Brock Adams (D-WA), Barbara Mikulski (D-MD) and Dave Durenberger (R-MN). The legislation would set uniform national standards for health care professionals and facilities that offer mammography services. The bill requires the HHS secretary to develop national quality standards for equipment, personnel, oversight, quality control and enforcement which are modeled after those of the American College of Radiology. The standards would affect all mammogram providers in states where less stringent or no standards are in effect. Thirteen states at present have mammography quality assurance laws. . . . **LAURENCE MARTON**, cancer researcher and chairman of the Univ. of California (San Francisco) Dept. of Laboratory Medicine, will become dean of the Univ. of Wisconsin Medical School. Marton, who will assume the deanship next spring, succeeds **Arnold Brown,** who retired June 30 after 13 years as dean. Brown is a former member of the National Cancer Advisory Board and was selected in 1976 by then-President Jerry Ford to be NCI director, but did not get a chance to serve since Ford lost the election to Jimmy Carter, who instead chose Arthur Upton. . . **AMERICAN COLLEGE** of Radiology announced its new officers elected at the ACR annual meeting recently: **James Moorefield** is chairman of the board of chancellors; **Carl Bogardus** is president, **Michael Lopiano** is vice president, and **Ronald Evens** is secretary-treasurer. **Thomas Meaney** and **Edward Webster** received ACR's highest honor, the gold medal. . . . **HAROLD FREEMAN,** chairman of the President's Cancer Panel, has been elected to a three year term on the board of directors of Fox Chase Cancer Center. Freeman is director of surgery at Harlem Hospital Center in New York. . . . **SCIENTIFIC WORKSHOP** in memory of the late **David Byar,** chief of NCI's Biometry Branch, will be held Nov. 7-8, at NIH Bldg. 1, Wilson Hall. To register, contact Jennifer Gaegler, 301/496-8556.

FDA Considers Improving Process For Secondary Indication Approvals

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other than that for which they were originally approved (**The Cancer Letter,** June 28).

FDA contended that several publications produced or sponsored by Bristol-Myers Squibb Co. promoted off label uses of six anticancer drugs, all of which have been approved for one or more indications. The agency also began to examine the promotion practices of other firms. FDA has the legal authority to control advertising and promotion of substances it regulates.

However, FDA's action ignored the fact that physicians are not limited to approved indications in prescribing drugs, and prescribing anticancer drugs for treatment of other than approved uses is widespread. Also, most cancer chemotherapy involves uses of drugs in various combinations, few of which have been specifically approved by FDA.

At that time, Chabner called the FDA's action "anti-intellectual, unrealistic, and inhibitory to technology transfer." He continued that, "If FDA is going to be hard nosed about company dissemination of research results, then it needs to devise a more rapid way for approving drugs for [additional indications]."

In a statement last week to the DCT Board of Scientific Counselors, Chabner said FDA Commissioner David Kessler announced his intention to strictly enforce the prohibition against company sponsored meetings or publications designed to promote off label use of drugs.

"Our clinical trials system depends on third party reimbursement to pay routine medical care costs; standard therapies such as cisplatin for small cell lung cancer may not be covered by third party carriers and if the FDA stance leads to tighter 'enforcement' by insurers this problem probably will be worsened," Chabner said. "Secondly we feel it is important to have company support for scientific meetings and conferences; NCI cannot afford to shoulder this responsibility on its own.

"The answer to this problem is to create a streamlined process for secondary approval of drugs for new indications, and secondly to update current drug labels in a timely fashion so that they reflect the state of the art of medical practice.

"I believe that the current drug labels for oncologic agents in many cases do not reflect the current state of practice in this specialty," Chabner continued. "With the changes in enforcement of promotional restrictions and the threats to reimbursement, it has now become imperative that labels reflect the current state of medical knowledge and practice.

"FDA staff are aware of this and are considering various options for streamlining and redefining the process for secondary approvals, including the use of outside expert panels and possibly a greater reliance on published trials and data tapes from unpublished studies. A flexible system will have to be devised, with data requirements that differ from one case to the next depending on the amount of published versus unpublished evidence of efficacy. We have and will urge our colleagues in the FDA to define in writing what evidence they will require and what special procedures they will invoke in considering drugs for secondary approvals. I believe such a document would be extremely helpful to drug companies and to academic and government scientists who are involved with the planning of clinical trials.

"There is no doubt that companies have not sought secondary approval in an aggressive manner, for the reason that the process itself is perceived to be complex and, frankly, of limited significance to the marketing of an agent. At least that was the case in the past. The FDA has actively involved NCI staff in their deliberations, and I have every confidence that new statements of policy will encourage such applications and will speed the process of secondary approval.

"Meanwhile, we are actively encouraging and working with companies to file for approval for state of the art secondary uses of antitumor drugs such as cisplatin for small cell lung cancer, and cisplatin with 5-fluorouracil for esophageal cancer."

Taxol update: In another drug development issue, more than 20 cancer centers are now signed up to treat selected refractory ovarian cancer patients with

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taxol, according to NCI's taxol referral center in the Cancer Therapy Evaluation Program. NCI last month released taxol on a compassionate use basis. One kilogram of the drug will be made available to centers this year and more in the future as supplies increase, Chabner said.

Chabner addressed the issue of fair pricing for taxol in the event it is approved, an issue raised by Rep. Ron Wyden (D-OR) in a congressional hearing last July. NCI's CRADA agreement with Bristol-Myers states that the firm will set a fair and reasonable price, but Wyden was concerned that NCI does not have the expertise to determine a fair price or to enforce the clause.

"Based on our recent experience with ddI [the recently approved antiviral drug for AIDS], also a BMS product, in which we insisted on a market price lower than that of the primary competitive product, we believe that BMS will set its price responsibly and consistent with that of similar products," Chabner said.

NCI Proposes New Intramural Facility For Cancer Prevention Research

NCI's Div. of Cancer Prevention & Control has proposed establishing an intramural prevention research facility close to the NIH campus in Bethesda for use by both NCI investigators as well as academic scientists.

The division's Board of Scientific Counselors gave unanimous concept approval to the proposal at its recent meeting and said the facility's establishment should be the division's highest budget priority.

DCPC Director Peter Greenwald said the proposal still has "a lot of steps to go through," such as NIH approval, but he welcomed the board's enthusiasm. "Since I've been at NCI--about a decade--our most critical need has been to build up prevention research," he said. "Within NCI, we're a tiny percentage of the intramural program. Establishing a facility like this is one way to build up the field and have a strong intramural and training program."

Investigators based at the facility would conduct "boutique-scale trials" that would provide extramural scientists with enough information to pursue ideas further, DCPC Deputy Director Barry Kramer told the board. NCI's Div. of Cancer Biology, Diagnosis & Centers is interested in joining DCPC and would help finance the facility.

NCI would lease an 80,000 square foot facility that would be built by a nearby institution. The design would cost about $300,000 and leasing would cost about $875,000 per year. Total operating costs are estimated at $12 million per year, which includes 102 full-time positions. DCPC would occupy 23,000 square feet and DCBDC would occupy about 2,000 square feet.

The concept statement further describes the facility:

This cancer prevention research center would bring together in one facility the broad range of expertise needed to address prevention research from basic biology to the development of applications and validation of techniques in population studies. At present, no such model exists specifically devoted to cancer prevention. The underlying premise is that a dedicated research facility that permits basic scientists, clinical scientists, and population oriented scientists to interact daily would accelerate the development of the tools for a prevention oriented approach to cancer control.

A major focus would be on the special problems involved in mass or high risk directed screening or population based preventive interventions. Center activities would concentrate on research frontiers in primary and secondary prevention of common cancers. These include the development of cancer markers for accurate and reproducible screening or for application in prevention trials as intermediate endpoints. Another major thrust would exploit novel mechanisms for interruption of malignant transformation and progression (including research on growth factors and vaccines). The scope of such a center would require an orientation which is not currently the emphasis at any single facility. A critical mass of resident and visiting investigators, sharing resources and ideas in "think tank" colloquia, would be a national resource in moving validated techniques from the molecular biology laboratory to community cancer prevention.

The research facility would house laboratory space, core computing activities, conference rooms, a library, and a research ambulatory care unit. The facility would represent basic research, clinical research, training and biometry, and would have core laboratories and animal facilities to support the facility.

The center would house a critical mass of scientists from a range of disciplines who might recognize in basic cancer biology, those techniques which promise the potential of primary and/or secondary intervention in human cancer. These scientists would include investigators in basic disciplines such as molecular biology, immunology, biochemistry; clinical disciplines such as oncology, pathology, physiology; and applied disciplines such as epidemiology, computer science, and statistics. An advisory committee would regularly review the direction and participation of the NCI intramural contributions to the overall program.

Participants would come from the intramural programs of DCPC and DCBDC, university cancer centers and schools of public health, sabbatical scientists from other institutions and federal agencies, and contractors.

Each of the tenant institutions in the facility would fund their research activities through their own independent sources. Scientists from NCI would be funded by intramural funding. Scientists from participating universities would be funded through traditional competitive grant mechanisms.

Several areas which have been identified as of particularly high priority within NCI will be addressed at the proposed facility: 1) cancer in women, 2) cancer in minority populations, 3) cancer vaccine research, and 4) lung cancer. Another major mission would will be to train members of minority groups in the field of cancer prevention research. Vaccine research and vaccines development against viral causes of cancer is also planned.

"What I find exciting is the synergistic effect, the

ability to rotate academic faculty through it," said board member Arnold Kaluzny. Said board member Maryann Roper, "For a program to grow it needs a national focus. I would urge that this concept be given the highest priority of any this board puts forward."

On the issue of funding, Greenwald said that if NCI got the Senate budget figure for FY 1992, DCPC would have the money for the facility. However, that amount probably will not receive full Congressional approval, sources watching the budget negotiations have told **The Cancer Letter.** In that case, DCPC would fund the facility in future year budget increments, Greenwald said. "We would give it the highest priority," he said.

The concept was approved unanimously.

DCPC Advisors Approve Expansion Of Science Enrichment Program

Advisors to NCI's Div. of Cancer Prevention & Control have given concept approval to expansion and decentralization of NCI's popular Science Enrichment Program. The Board of Scientific Counselors also gave concept approval to a study of diet in members of the American Assn. of Retired Persons, as well as one new grant program and the reissue of an RFA on chemoprevention studies.

On another concept, for $1.8 million in two year contracts for a study of the effect of gender, smoking status and alcohol ingestion on plasma carotenoid levels, the board unanimously voted to ask NCI staff to revise the study for future consideration by the board. The board took the action when it became clear that there were so many questions about the study that it would not win approval.

The board also approved $450,000 for a contract to continue follow up of participants in the Breast Cancer Detection Project, which also is funded by the Div. of Cancer Etiology. The DCE board approved the concept in May.

Following are texts of the approved concepts:

Science Enrichment Program. New RFP concept, total $2 million per year, four awards, four years. This concept seeks to continue the implementation of NCI's Science Enrichment Program through the establishment of up to four regional SEPs within the U.S. These regional programs will encourage underrepresented minority and underserved high school students to select careers in science, mathematics, and/or research by:

A. Providing an opportunity for students to have "direct" experience in the fields of science, mathematics, and laboratory research by providing "hands-on" experience using resources (such as a supercomputer, intramural laboratories, state-of-the-art supplies, etc.) that extend far beyond the usual high school classroom instruction.

B. Providing students within an "I-can-do-it" feeling of achievement in the sciences.

C. Contributing to the development of a strong core of researchers for the future.

In 1989, the Science Enrichment Program was developed as a two-year pilot program by NCI for the purpose of addressing the critical need to replenish the supply of scientists and researchers that will be required for future biomedical research. The long-range goal of this program is to encourage underrepresented minority and underserved youth--namely, African-Americans (American Indians, Alaska Natives, and Native Hawaiians) as well as individuals from low-income backgrounds, to pursue professional careers in science or research.

During July and August 1990, the first six-week resident program was conducted at Hood College in Frederick, MD. Approximately 107 nationally selected incoming 10th grade students participated and came from 25 states as far away as Hawaii and Alaska. In the summer of 1991, the second pilot year was a five-week program conducted at Hood College. A total of 145 incoming 10th grade and 12 returning students participated. The latter students served as peer counselors. There were nearly equal numbers of males (69) and females (76). Students were recruited from about 30 states (including Alaska and Hawaii) plus American Samoa and the District of Columbia. Students, faculty, and staff lived in the on-campus dormitories.

Preliminary analyses of students' scores from tests delivered before and after participation in the program indicate the following:

--Student knowledge in a variety of math and science areas increased 20 percent.

--Student interest in taking elective coursework in science and mathematics increased. The number of students stating that they would elect to enroll in a course in physics increased 400 percent. The number of students indicating an interest in additional classes in anatomy and chemistry increased 50 percent for each subject.

--Student interest in pursuing a scientific or research career increased. The number of students stating that they would like to pursue a career in physics increased 117 percent. Interest in pursuing a career in chemistry increased 75 percent. Interest in pursuing a career in veterinary medicine increased 350 percent.

--Student interest in research-related careers increased. The number of students stating that a career in chemistry sounded interesting increased 73 percent. Interest in a career in zoology increased 60 percent. Interest in a career in physics increased 47 percent.

--Student confidence in scientific and mathematic abilities increased. After participation in SEP, 72 percent of the students considered themselves able to "do science" very well, an increase in nearly 17 percent. Almost 62 percent of the students thought that they could "do math" very well at the end of the program.

The primary purpose of this initiative is to support the establishment of up to four regional, summer residential Science Enrichment Programs which meet the goals, objectives, and implementation standards of the two-year national Science Enrichment Program.

The comprehensive nature of the Science Enrichment Program requires that applicant organizations integrate many diverse elements such as:

--A curriculum covering topics in biology, chemistry, computer science, language arts, mathematics and physics;

--The availability of appropriate scientific researchers/ investigators with whom students can be assigned to;

--The availability of appropriate laboratory facilities for individual and group research projects;

--The availability of special seminars, educational field trips and extracurricular activities;

--The availability of administrative and support staff including

project manager, coordinator, clerical, instructional aides; resident hall counselors, and recreation leaders;

--The availability of on-campus dormitories, cafeterias.

--The availability of adequate campus security; and

--The availability of medical coverage.

Applications will be accepted from institutions within the U.S. High schools, colleges and universities, as well as cancer centers or schools of public health are some of the eligible potential applicants. Applicants will be asked to thoroughly define their geographic region, target population as well as other details--such as curriculum, advertising, student recruitment, faculty recruitment, bed and board arrangements--in their submission.

Applicant organizations must demonstrate the ability to organize and administer this type of multidisciplinary science education-oriented program whose structure may require linkage to other programmatic components of the parent and/or collaborating institutions. In addition, applicant organizations will be urged to include the broadest possible representation of minority and underserved groups.

Each organization will be responsible for the recruitment and selection of students and faculty, procedures for the selection of research and science education activities, scientists and mentors for students, and evaluation of student progress. The NCI will specify the overall goals, objectives, eligibility requirements, and review criteria.

Finally, applicant organizations will be asked to provide a detailed evaluation plan and student tracking plan. Applicants will also be encouraged to establish "school year" mentoring programs for students within their region.

Claudia Baquet, director of NCI's Cancer Control Science Program, said potential respondents to the RFP could be cancer centers, universities, or schools of public health, or even high schools in conjunction with a cancer center. NCI will provide a "how-to" manual to successful applicants. The RFP will be on an "expedited track" and awards would be made by next April, she said. DCPC Director Peter Greenwald said other NIH institutes have expressed interest in joining NCI on the project, but no commitments have been made. NIH Director Bernadine Healy is said to support making the project a "trans-NIH" effort, but, Baquet said, "How to do that remains to be worked out."

Board members were enthusiastic about the concept; Shirley Lansky said some provision should be made for the program to continue beyond the funded period. Others were concerned that the awarded institutions have truly high caliber facilities.

"I am extremely pleased NCI is taking the lead on this," said board Chairman Alfred Haynes.

The concept was approved unanimously.

Appalachia Leadership Initiative on Cancer (ALIC). New proposed RFA (cooperative agreement), total $4 million per year, up to four awards, over five years. This concept will establish a structure for the delivery of cancer control outreach programs to Appalachian communities through the establishment of up to four cancer control outreach areas.

Appalachia is a 195,000 square mile region that follows the spine of the Appalachia Mountains from southern New York to northern Mississippi. It encompasses 398 counties, and includes all of West Virginia and parts of twelve other states: Alabama, Georgia, Kentucky, Maryland, Mississippi, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, and Virginia.

According to the 1990 census, nearly 20.7 million Americans reside in Appalachia. Fifty percent of Appalachians live in just 3 states: Alabama, Pennsylvania, and Tennessee. The region is substantially homogeneous in racial composition, with whites making up 91.2 percent of the population. Blacks are the second largest racial group with 7.3 percent and all other races account for less than I percent. Two thirds of the region's Black population live in metropolitan counties.

Existing data on cancer incidence and survival in Appalachia are very limited, especially in the Southern Highlands. Since there are no standardized cancer registries in the region, cancer incidence data are unavailable. However, the data indicate that mortality rates from some cancers in Appalachia are higher than the national average and that they may be increasing at a faster rate than for the U.S. The data also suggest that use of tobacco products by this population is higher than in the rest of the country, and that preventive health behaviors and access and utilization of quality health services is lower.

The purpose of the ALIC is to establish up to four cancer control outreach areas for the development and delivery of cancer control outreach activities to Appalachian communities. Each awarded institution will organize and initially support an area office to be staffed by a full-time community coordinator and relevant support staff. The coordinators will facilitate the establishment of coalitions within the areas and interact with them. A National Steering Committee will be established to advise the National Cancer institute after the awards are made.

ALIC outreach activities will involve but are not limited to: 1) cancer data collection; 2) cancer information dissemination and education; 3) mobilization of Appalachian local and state leaders to address cancer issues in Appalachia; 4) building coalitions among established Appalachian health related organizations, infrastructure health care systems, colleges or universities with significant Appalachian student enrollment, the business community and other relevant community-based organizations using a system-wide approach; and 5) assessing the efficacy of cancer prevention and control outreach activities as well as evaluating their impact on specific Appalachian communities.

This outreach initiative will advance through two phases: Phase One--Local and area-wide planning and coordination of outreach resources and contacts; Phase Two--Implementation and evaluation of an area structure and outreach activities.

Within each of the four areas, the ALIC will design, implement, and facilitate a wide variety of activities (e.g., training of volunteers; recruitment of key staff and community lay and professional leaders; coalition building; cancer awareness media campaigns, etc.) to promote cancer prevention and control in Appalachian communities.

Phase I: Planning and Coordination. During the first 12 months of the project, area plans for community interventions will be developed. Qualified staff will be hired. Each area office will be staffed by a full-time community coordinator and relevant support staff. Within each area a prominent leader in the Appalachian community will serve as the Area Chairperson. A comprehensive strategy with time schedule and milestones will be formulated to facilitate the development of community coalitions, implementation of cancer awareness and education programs and collection of cancer risk factor and control information. This phase will have the following objectives:

a. To develop a plan to identify and recruit potential

organizations and local leaders who could help form and support community coalitions to implement dynamic and creative outreach activities.

b. To establish a communication system that allows for the regular exchange of ideas between key staff members and the staffs of local Appalachian leaders, organizations, and coalitions.

c. To develop a plan for outreach strategies and activities which coalitions and organizations may adapt and implement at the local level.

d. To develop a plan for monitoring ALIC-sponsored cancer prevention and control activities and assessing their impact upon Appalachian communities including a detailed recordkeeping system of the quantity and quality of activities.

Phase II: Implementation and Evaluation. During the second year of the project, implementation of outreach activities will begin according to the comprehensive strategy and time schedule developed in Phase I. Progress towards the planning, implementation and evaluation will be measured by milestones. The third, fourth, and fifth years will be a continuation of the activities created in years one and two. Coalitions and outreach activities will be monitored for quality and outcome effects.

NCI staff said this concept was patterned after the National Black Leadership Initiative on Cancer, which then gave rise to a similar initiative for hispanics. Board member Maryann Roper said the black leadership initiative, which grew out of a discussion at a National Cancer Advisory Board meeting, "caught on" because there were groups in place "waiting in the wings" to respond. Without any similar structure in place in Appalachia, Roper asked, "Whose door are we going to knock on and say, Please apply?"

NCI staff members said they had had a number of phone calls and conversations with people interested in the project.

The concept was approved unanimously.

A Prospective Cohort Study of Diet and Cancer In Members of the American Association of Retired Persons (AARP). New proposed RFP, $6.65 million over six years, approximately six awards (one data coordinating center, five state cancer registries). The objective of this study is to examine prospectively the relation between diet and major cancers (especially those of the breast, large bowel, and prostate) in a population of early-to late-middle aged men and women in the U.S. In order to minimize two problems that historically have plagued observational epidemiologic studies of diet and cancer--dietary measurement error and dietary homogeneity--this study will be large and will oversample screenees within extreme categories of dietary intake.

In the area of diet and cancer three serious potential limitations of nutritional epidemiologic studies have been noted (15,16): 1) biases in case-control studies; 2) dietary assessment error; and 3) insufficient range in dietary intake. Because of the potential biases inherent in the case-control design, it is questionable whether further case-control studies of diet and cancer will advance the field. Prospective cohort studies avoid both the recall/reporting and selection biases described above. If the cohort is large enough, then both the measurement error and dietary homogeneity problems can be minimized. Because the effect of measurement error is attenuate true relative risk, sample size calculations can be made on the basis of the attenuated (observed) relative risks. Estimates of the extent of measurement error are available from a number of dietary assessment methodologic studies. Our approach to the dietary homogeneity problem is to screen a large number of persons and then include in the cohort all persons within the "extreme" categories of dietary intake (say, less than 25% and greater than 47.5% calories from fat) and a random sample of persons in the other categories.

This prospective cohort study, based on the collaboration between NCI and the AARP, will be carried out in several states in conjunction with state cancer registries. Investigators from the Cancer Prevention Studies Branch and the Biometry Branch have collaborated with Robert Hoover and other investigators from the Environmental Epidemiology Branch, Div. of Cancer Etiology in the design of this study.

The cohort will be drawn from the AARP membership, both women and men, aged 50-69. Sixty-four percent of the AARP membership falls within this age range, with the proportions varying somewhat across states.

In order to provide a power of 90% for detecting a moderate true relative risk gradient (RR=1.64 for>47.5% versus<25% calories from fat) in a common malignancy like large bowel cancer, a sample size of 350,000 is required (175,000 women, 175,000 men). A cohort of this size would also have approximately 90% power to detect similar risks for breast cancer in women and prostate cancer in men. The assumptions and risks for breast cancer in women and prostate cancer in men. The assumptions and calculations underlying this sample size estimate are contained in the Appendix.

Dietary Assessment. The primary data collection instrument will be a food frequency questionnaire (FFQ) modified to capture a broad range of key nutrients and foods. This will likely be a version of the NCI/Block questionnaire.

Pilot Studies. Initially we will mail 2000 questionnaires to AARP members in several designated states and administer food records to a subset (n=200) of this group who return their questionnaires. The purposes of this first mailing and the food records sub-study are to 1) determine the response rate for the mailed questionnaire, 2) confirm the proportions within extreme intake categories, and 3) correlate the FFQ against food records, to provide needed data for the final sample size determination.

Initial Mass Mailing. To obtain a sufficient number of study participants within the extreme intake categories, we expect to mail the baseline questionnaire to approximately 3.5 million AARP members. On the basis of the response rate of an earlier AARP health study (24), we estimate a questionnaire response rate of 50% (resulting in 1.75 million respondents).

Cohort Construction. A key objective in assembling this cohort is to select study participants with sufficient dietary heterogeneity for key nutrients and foods (e.g., percent calories from fat, number of servings of fruits and vegetables daily, etc.). Respondents indicating that they are on special diets or have chronic diseases likely to have affected dietary status will be ineligible for the cohort. We estimate that approximately 20% of respondents will be ineligible (17% of respondents in the 1982-4 NHANES Follow-up Study report being on a special diet [25]), resulting in 1.4 million eligible respondents. We will select all eligible respondents reporting intake within extreme intake categories. A sample of respondents from the other intake categories will be selected. The final sample size is 350,000, half men and half women.

Minority Sub-Cohort. AARP has been actively seeking to increase minority membership over the last few years. If the proportion of minorities in the final cohort were similar to that for the current AARP membership as a whole (7%), then our cohort construction process would result in a sub-cohort of 24,500 (7% x 350,000) minority AARP members. Because the initial mass

mailing will generate some 98,000 (7% x 1.4 million) questionnaires from minority AARP members, it will be possible to oversample minority respondents to create an even larger minority sub-cohort. We are unaware of any other minority cohort study in this country of this magnitude.

Tracking and Endpoint Ascertainment. The follow-up period is five years. State registries will provide the primary means of cancer endpoint ascertainment. Participating cancer registries must demonstrate a minimum coverage rate of 90% and must maintain an active quality control program.

Census figures indicate that mobility is relatively low among persons 50-69 years of age in the U.S. (26), but there will be some migration out of states with registries. For migrants and others falling outside the state registry umbrella, we will use an active tracking procedure with record tracing. A short questionnaire will be sent to each cohort participant at the end of the follow-up period. We expect that less than 10% of cohort participants will fall outside the registries.

For mortality endpoints we will use the National Death Index. We may also be able to link the cohort with national Medicare data in order to investigate non-cancer endpoints.

Biologic Specimens. The establishment of this cohort may provide the opportunity to collect biologic specimens in a relatively cost-effective manner. These specimens could be useful in evaluating a number of hormonal and genetic as well as nutritional hypotheses.

Board member Ross Prentice said he thought this study is important, but it does not address "the fundamental problem of measurement error. It is not going to correct the problem. We simply don't have adequate methodology." Prentice said a more detailed discussion of this issue is necessary. He also said several similar cohort studies have been proposed by investigators "who keep not getting funded by study sections."

Greenwald said NCI staff would work on more detailed development of the study, and invited Prentice to take part. "It is state of the art and I have faith in the investigators involved," Prentice said. But he cautioned that, "We should be slow to approve such studies unless there are very detailed plans. Investigators are expected to produce detailed plans and we shouldn't expect less from intramural scientists."

Board member Rumaldo Juarez said he was concerned about the relatively low number of minority and low income AARP members. In addition, he said, is the issue of using the National Death Index. "As far as hispanics, you can just forget it." The study, he said, "will be based on non-minority elderly." He noted that a major study of aging by the National Institute of Aging was criticized for not including minorities. "I see NCI setting itself up for the same kind of criticism," he said.

Greenwald said NCI staff did not present all of the information available, and that a technical review committee would work on the study.

Board member Helene Brown agreed with Juarez and suggested that NCI staff work to address the problems and bring it back to the board. Others suggested a feasibility study.

Greenwald said he agreed that "we need to have substantial numbers" of minorities in the study, but urged the board to approve the concept.

"I think this is the best of the concepts in this round, and there is no point in going slowly," said Prentice. "I'm prepared to go ahead with it. Our comments have been heard."

The board voted to approve the concept, with Juarez and Brown opposed.

Prevention Clinical Trials Evaluating Intermediate Endpoints and Their Modulation by Chemoprevention Agents. Reissue of RFA (cooperative agreements), $3 million per year for three to five years. The major objective of this concept is to encourage cancer chemoprevention clinical trials which use biochemical and biological markers to identify populations at risk and/or to provide intermediate endpoints that may predict later reduction in cancer incidence rates. A second objective is to stimulate and facilitate chemoprevention clinical research.

In the past five years a similar RFA announcement has resulted in approximately 30 applications each year of which 2-4 have been funded. Because of the difficulties in obtaining agent, formulation, packaging and obtaining investigational drug permits from the FDA many investigators who otherwise would not consider such an undertaking have applied for and entered into prevention clinical trials program.

The main emphasis should be on small, efficient studies aimed at improving future research designs of chemoprevention trials, providing biologic understanding of what is happening in the trials, or providing better, more quantitative and more efficient endpoints for these trials. Intermediate endpoints or biomarkers that are directly associated with the evolution of neoplasia, and develop with much higher frequency in abnormal cells of susceptible individuals than do the actual tumors, make it possible to carry out many studies on fewer subjects for shorter durations. If such biomarkers were found to be modified by a particular intervention regimen in short-term studies, a rationale would be provided for carrying out long-term studies.

The proposed RFA would support studies which are directed toward examining the role of various biological and/or biochemical markers in assessing risk or modulation by chemopreventive agents. One or more intermediate endpoints might be evaluated initially to determine baseline parameters, and subsequently to serve as a follow-up after the administration of the chemopreventive agent in vivo and/or in vitro.

These studies can be developed in phases, including a pilot or developmental phase and a full scale intervention phase. If it is determined that an intervention successfully fulfilled the biological, biochemical, and statistical criteria established in a pilot study, it then might be justified to consider expanded studies on more subjects for longer durations, measuring more advanced states of neoplasia. This announcement solicits applications for pilot studies, which would be expected to last up to three years, full scale intervention studies or a combination of the two. After successful completion of the pilot phase and a demonstrated modulation of marker endpoints in a direction characteristic of lower risk of neoplasia, phase III clinical trials with a defined monitoring test system and a cancer incidence or mortality

endpoint could be implemented.

Short term chemoprevention clinical trials that evaluate the effect of innovative biomedical monitoring tests in high risk populations are sought. These tests might be useful to determine an intermediate endpoint, serve as a basis to assess risk or response to a chemopreventive agent, identify high risk groups, or increase the power to detect the risk or the response to chemoprevention. Modulation of effects by the chemopreventive agents on tests which are indicative of neoplastic progression may be an early indicator of efficacy.

Biological fluids including urine, blood, sputum, and feces would be obtained from participants for analysis. Examples of populations suitable for such interventions may include subjects with preneoplastic lesions, subjects previously exposed to an identified carcinogen, or those curatively treated for a malignancy who are at high risk for the development of a second malignancy. Effects on tests by the chemopreventive agent might be highly significant in relation to ultimate cancer prevention. Priority for intermediate endpoint studies would be given to interventions which do not overlap or duplicate currently funded projects (e.g., beta-carotene and non-melanoma skin cancer).

Greenwald said this RFA has been the "key driving force in helping the chemoprevention program." Board members also supported the concept, and suggested doubling the amount that the Chemoprevention Branch had requested, $1.5 million per year.

Greenwald said that under the original budget, if good proposals came in just under the payline, they could be funded by exception. But project officer Marjorie Perloff commented that, "It is very difficult to run a program by exception. You are constantly begging for money and justifying proposals that have gotten good reviews."

The board approved the concept unanimously and doubled the funding to $3 million per 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 Executive Plaza South room number shown, National Cancer Institute, Bethesda MD 20892. Proposals may be hand delivered to the Executive Plaza South Building, 6130 Executive Blvd., Rockville MD. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NICHD-CRE-91-13

Title: Breast cancer and the birth control pill: case control study of premenopausal and past oral contraceptive use (field centers)
Deadline: Approximately Feb. 1

The Contraceptive & Reproductive Evaluation Branch of the Center for Population Research, National Institute of Child Health & Human Development, requires information on the relationship between oral contraceptives and breast cancer among women in the age range of 40-64 years. The NICHD is seeking organizations capable of serving as field centers for a population based, multicenter, concurrent case control study of breast cancer and oral contraceptives.

Each field center (five to seven awards are anticipated) must be capable of designing and conducting an epidemiologic study that will recruit a minimum of 750 cases of breast cancer among women in the age range of 40-64 years, obtain reproductive, medical and family histories, and retrieve pathology material. There will be an opportunity for biological specimen collection and in depth pathology review.

Offerors must have expertise in contraceptive epidemiology and large collaborative case control studies. Emphasis will be placed on the ability of the offeror to recruit adequate numbers of subjects. Additional consideration will be given to field center offerors having expertise in clinical pathology and laboratory management. The government estimates the effort at each of the field centers to be approximately 22 technical staff years over a performance period of six months.

Copies of the RFP may be obtained by sending a written request (include self-addressed label) to Paul Duska, Contracting Officer, Contracts Management Branch, OGC, National Institute of Child Health & Human Development, Executive Plaza North Rm 610, 9000 Rockville Pike, Bethesda, MD 20892. Requests also may be made by fax to 301/402-0915.

RFP NIH-ES-92-14

Title: Studies to evaluate the toxic and carcinogenic potential of retroviral vectors in laboratory animals
Deadline: Approximately Dec. 3

The National Institute of Environmental Health Sciences is soliciting proposals from offerors having the capability to conduct studies to evaluate the toxic and carcinogenic potential of retroviral vectors in laboratory animals for the National Toxicology Program. This project will be separated into two phases: In phase 1 the resources of the contractor will be used to demonstrate proficiency in the preparation of frozen histological sections and in the performance of the x-gal assay prior to beginning the prechronic studies. The prechronic studies will determine what exposure regimen maximizes the probability of vector insertion and evaluate methods of monitoring for the presence of vector derived DNA in selected tissues. The phase 2 project is optional and will only be conducted after results from phase 1 have been evaluated and approval to proceed has been granted by the NTP.

The chronic study will evaluate the carcinogenic potential associated with random insertion of a retroviral vector into cellular DNA or organs and tissues of F344 rats and B6C3F1 mice. The government will determine at the end of phase 1 whether phase 2 studies will use weanlings or will require the breeding of neonates. The government estimates that the phase 1 portion of the project will last approximately 21 months, including review time, and will require approximately 2,841 senior professional manhours, 3,041 professional manhours, and 13,480 technical manhours. Phase 2, if approved, will have a duration of approximately 37 and 1/2 months and will require approximately 2,700 senior professional manhours, 3,000 professional manhours, and 24,650 technical manhours.

If breeding neonates is required, the government estimates that phase 2 will require one additional month and 130 senior professional manhours, 130 professional manhours, and 850 technical manhours in addition to the phase 2 estimates cited above. An option for phase 2 will be included in the contract. It is expected that one contract will be awarded for a 21 month period, with an option for 38 and 1/2 months.

Requests for the RFP may be sent to Donald Gula, Contract Specialist, Contracts & Procurement Management Branch, NIEHS, 79 T.W. Alexander Dr., 4401 Research Commons Bldg., PO Box 12874, Research Triangle Park, NC 27709.