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Kessler Promises Cancer Patient Liaison In FDA; Considers Joint Drugs, Biologics Oncology Review

FDA plans to establish a liaison office for cancer patient organizations in response to requests for better communication with the agency, and is considering combining the review functions of two centers that oversee cancer drugs and biologics, FDA Commissioner David Kessler has said.

Kessler and other high ranking FDA officials met with representatives from more than 20 cancer patient organizations recently to develop a format for more frequent communication, and to discuss a variety of

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In Brief

Painter Is AMA President-Elect; FDA Approves Taxol IND; Protocol Enrolls 150-200 A Month

JOSEPH PAINTER, vice president for health policy, Univ. of Texas M.D. Anderson Cancer Center, was recently elected president-elect of the American Medical Assn. He has served as chairman of the AMA Board of Trustees since June 1990, and has been a member of the board since 1984. Painter is an authority on cancer control. . . . **TREATMENT IND** application has been approved by FDA for NCI's Treatment Referral Center protocol for taxol in advanced metastatic ovarian cancer. The protocol is available only though 40 designated cancer centers, and is currently enrolling 150 to 200 patients per month since it was activated earlier this year. Physicians seeking information for their patients may contact the center at 301/496-5725. . . . **EVAN HERSH**, co-director of Arizona Cancer Center's clinical oncology research program, received the Jeffrey A. Gottlieb Memorial Award from the Univ. of Texas M.D. Anderson Cancer Center, recognizing outstanding achievement in cancer therapeutic research. . . . **ELIN SIGURDSON** has been named director of surgical oncology research at Fox Chase Cancer Center. She was assistant attending surgeon at Memorial Sloan-Kettering Cancer Center. . . . **ERNEST MARSHALL** has joined the Univ. of Alabama at Birmingham Comprehensive Cancer Center as director of the clinical studies unit. He succeeds center deputy director **Richard Wheeler**, who served as clinical studies director for nearly 10 years. Marshall was medical director of the Barrett Cancer Center protocol office. . . . **DISTINGUISHED YOUNG** Researcher Award has been given to **Staley Brod** and **David Carbone** by the Univ. of Texas Southwestern Medical Center at Dallas. The award includes a $40,000 grant to support research and is given annually to a young faculty member; this was the first year two awards were given. . . . **STEPHEN EDGE**, Univ. of Virginia, has been appointed head of Roswell Park Cancer Institute's Div. of Breast Surgery.

FDA To Establish Liaison Office For Cancer Patients, Combine Review

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issues including the drug approval process, information dissemination, drug reimbursement, and secondary uses of approved cancer drugs.

Kessler promised to draft a proposal by Labor Day for a cancer liaison office and seek the groups' comments.

Beverly Zakarian, president of Cancer Patients Action Alliance (CAN ACT), said the July 31 meeting was a direct result of her organization's "efforts over the last two and a half years."

Zakarian presented a "consensus statement" she said was the result of a meeting earlier last week of the organizations that met with FDA. She said the groups seek:

▶Permanent representation at the agency, akin to FDA's Office of AIDS Coordination, which performs liaison with AIDS patient advocates.

▶A more efficient and more responsive drug approval process. "We look for increased access at the front end of the process, with closer post-market surveillance," she said. Cancer patients are more willing than others to take risks "to have the chance of the benefit," she said later.

▶Resolution of the problem of health insurance reimbursement, which, Zakarian said, is "a direct result of the train of events set in motion by the agency's action against off-label drugs."

"Up till now there has been great concern about the sincerity of the agency's recognition of our complaints," Zakarian said to **The Cancer Letter** after the meeting. "We are hoping that this is for real, it is not PR. We haven't begun to discuss substantive issues."

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FDA, she said, "has been slow to respond, has an entrenched mindset against patient involvement, and the Commissioner is not the only person who has to believe that patients have valid points of view."

On the issue of patient representation within the agency, Zakarian said, "I think we got as much as we could have hoped for, which was a tangible proposal. Patient representation means the agency will be responsible to patients for their actions."

The meeting, she said, "was all so friendly and non-confrontational."

Kessler: 'Commitment To Cancer'

"I know there have been concerns in the past about responsiveness," Kessler said in his opening informal talk with the patient advocates. "Let me assure you that we recognize that you are dealing with life and death issues. Sometimes there is a lack of communication; it affects us. We are not a bunch of green eye-shades whose job it is to keep important drugs off the market. The notion that we want anything less than what you want--we have to dispel that. You have our attention.

"Our commitment to cancer and getting drugs for cancer shall be no different than finding cures for any other disease; no different than our commitment to AIDS, no different than our commitment to Alzheimers."

FDA officials spent most of a day briefing the organizations on aspects of the agency's work, but Kessler said the meeting was not intended as "a dog and pony show."

"We need to listen to your concerns," he said. However, he said the agency also needs to "explain itself" better to patients. "When an agency gets beaten up for things that are not fair or not true, it makes a difference on the people here who are trying to do their jobs," he said.

Kessler noted that the average review time for an oncologic drug--the time from Investigational New Drug submission to approval of a New Drug Application--has fallen from 30 months to about eight months. Currently, there is no drug approval backlog, and no efficacy supplements are awaiting approval. Between 1975 to 1985, FDA received one new oncologic IND application every two years; now the agency reviews two new oncologic drugs every year.

"We don't do research, we don't do drug discovery; we are only as good as the applications that come in," Kessler said. "If you want to get a drug out quickly, the only thing that works is early involvement of the agency with the sponsor. The only reason we got the review time down was that we are not waiting for someone to plop an application on our desk. We are

much more involved in the drug development process."

Last year, FDA began a crackdown on advertising by drug sponsors to promoted unlabeled uses of drugs (**The Cancer Letter,** June 28, 1991). The campaign began with FDA's contention that a publication sponsored by Bristol-Myers Squibb Co. "promoted the use of six drugs for unlabeled uses," Kessler said.

"The reason we took action against that publication ("Oncology Commentary '90") was that it purported to be something it wasn't," Kessler told the cancer patient organizations. "It didn't have the drug company's name on it. In the admission of the company, it used 'paid agents' whose data and opinions favored their product. We object to promotional materials that don't have balance."

The FDA action "was not an attack on unlabeled uses," Kessler said. "We're trying to get more uses onto the label."

Considering Joint Oncology Review

Kessler said he is considering establishing a "joint oncology review program" that would combine certain elements of FDA's Center for Drug Evaluation & Research, which reviews oncologic drugs, and the Center for Biologics Evaluation & Research, which reviews biologics related to cancer treatment.

"It's an important step for the agency," Kessler said. "It would combine and make better use of resources. What we've found is the two different review divisions don't always work together."

Over the next "couple of months," Kessler said, FDA will "look at cementing both groups together."

First In A Series Of Meetings

FDA Deputy Commissioner for External Affairs Carol Scheman said the meeting with cancer patient organizations was planned as the first in "a series of large and small meetings." She called the first meeting "FDA 101," designed to "dispel the cloud of mystery that surrounds FDA."

Scheman's office was created last fall to bring together five offices, including public affairs, legislative affairs, health affairs, consumer affairs and trade affairs, and is the "focal point" for public participation.

NCI's Cancer Therapy Evaluation Program Director Michael Friedman said NCI also is planning a meeting with cancer patient organizations with a particular emphasis on breast cancer within the next few months.

Other speakers at the meeting included:

▶Randolph Wykoff, director of the Office of AIDS Coordination, discussed the "lessons" FDA and AIDS activists learned in dealing with one another over the past several years. He encouraged cancer activists to use some of the same tactics used by AIDS activists. However, while protests and "burning of FDA commissioners in effigy" get attention, Wykoff said, "recognize that change is due to things like sitting around tables and talking quietly."

Wykoff listed the "12 most important lessons FDA learned, the AIDS activists learned, and those we learned together":

Lessons FDA learned: 1. The agency has to be accessible. 2. FDA has to be willing to change. 3. FDA owes patients an explanation about the underlying science that led to a decision. 4. There is a time to bend and a time to stand strong; we cannot always agree.

Lessons the activists learned: 1. Lay the blame at the appropriate doorstep. You have an obligation to learn what FDA controls and what it doesn't. 2. You have to send your best people to the table; leave the strident protesters at the door. 3. Build consensus; "AIDS activists learned this and forgot," Wykoff said. "Over the past 12 months they have been unable to build consensus." 4. FDA is comprised of individuals and responds to the same courtesy and cooperation as others.

Lessons learned together: 1. FDA is not the enemy; it is in the same struggle to find cures. 2. Neither side is always right or wrong. 3. We have a tough challenge in front of us and we have to address it together. 4. The best public health comes when we work together.

▶Jane Henney, deputy commissioner for operations, in her job for six months, provided an overview of the agency's organization and discussed the agency's process of reviewing data and data quality for new drugs. "I would like to underscore the value of relying on a strong science base in our reviews." At Univ. of Kansas, where she worked prior to joining FDA, Henney taught a course for medical students on clinical trials design. "I used to tell students that it is very easy to read an article, but you should look carefully at words like 'survivors' and 'morbidity.' Attach faces rather than numbers to those words.... We would take words like 'adverse effects' and talk about vomiting and what it feels like if it happens 50 percent of the time. The drugs you give have important lifesaving properties, but in terms of adverse effects you need to feel the words you read."

FDA's product reviewers "can have the same powerful impact with products. Review can be as important as taking care of an individual patient. I'm proud to say the reviewers we have feel the passion, the responsibility, so that when the products are put out on the market, they will be safe, will be effective."

Henney told the cancer patient activists, "We need you--on our advisory committees, for public testimony

at committees--we need to hear from you."

▶Paula Botstein, deputy director, Center for Drug Evaluation & Research, oversees five divisions, including the Div. of Oncology and Pulmonary Drug Products. "We feel a sense of urgency" with cancer drugs, and staffing in the division has increased, she said. "We've made major progress, but we know we have a ways to go."

▶Gregory Burke, director of oncology and pulmonary drug products, Center for Drug Evaluation & Research, said, "We've been reviewing oncology drugs as fast as we can." The division, he said, tries to work with sponsors to "expedite problem solving," and encourages submission of NDAs after phase 2 studies in refractory disease. He invited comments on the joint NCI/FDA "white paper" on surrogate endpoints ("Journal of Clinical Oncology," Dec. 1991), and provided his fax number: 301/443-9284.

▶Janet Woodcock, director of investigational new drugs, Center for Biologics Evaluation & Research, said the approval process for biologics is similar to new drug approval. Delays in review can take place when the quality of the application is poor and FDA has to send it back to the company, or when the manufacturer is unable to make the product consistently, she said.

▶Michael Taylor, deputy commissioner for policy, said FDA's philosophy has shifted from "protecting the public from bad things to helping the public get good things."

He also addressed the issue of off-label prescribing of approved cancer drugs: "We want to put to rest the impression that FDA is opposed to this practice; that's simply not the case," Taylor said. "Physicians always have used their judgement. FDA recognizes that the practice is often essential and sometimes used in conjunction with approved uses."

However, he said, the practice "does pose difficult questions about the flow of information to physicians. Even the label does not have all the information necessary." He said he recognized there is "tension between getting information out and the legal prohibition of drug company promotion of unapproved uses. We've been trying to clarify these lines so the flow of information won't be impeded."

Questions For NCI, FDA

Following are some of the questions the cancer patient advocates asked:

▶How to increase access to clinical trials for minorities? NCI's Friedman said the question is important, but that NCI "does not see trials as a means of access to health care per se." The scientific reason for ensuring access for minorities is "to make sure that effective treatment for white patients is also effective for minority patients."

▶How does NCI deal with distrust of research in minority populations? "The way we've chosen to deal with it is to put research dollars into the hands of minority researchers and institutions, and rely on ingenuity at the local level," Friedman said.

▶What can activists do about third party refusal to pay for ancillary care costs in clinical trials? "We maintain that care costs have to be borne by the provider. We try to work with insurers to identify trials that do represent the best care," Friedman said. The strategy should be to continue discussions with insurers. He noted that, "the faster drugs are approved, the simpler it becomes. We maintain that more is learned about a drug after it is approved than before."

Friedman said FDA has proposed "rapid secondary approvals when the data permit," which would help in solving the reimbursement problem.

"FDA is giving credence to insurers by saying drugs should have secondary approvals," said Frances Motley, Liaison Services and Patient Advocacy, of Hampton, VA. She said Virginia Blue Cross refuses to pay care costs for patients receiving taxol.

"The issue is, what is the first endpoint to get a cancer drug onto the market," Kessler replied. "If you say, 'Just put the drug out there and the company can market it for anything,' how do you ensure that the studies get done?"

"Make their compassionate care programs conditioned on getting the data," Motley said.

Kessler said when he was a medical intern, one of his patients was a 5-year-old with Wilm's tumor. The patient's insurance company refused to pay for outpatient treatment, but would pay for the same treatment if the patient was hospitalized. "We've all been through these kinds of battles," he said. "I don't want to end up with less data in the end to find out if a drug works."

Eugene Schonfeld, National Kidney Cancer Assn., said FDA should approve drugs and require phase 4 studies instead of requiring secondary approval. "These issues can be addressed if the agency gets creative about it," he said.

"We've thought about it," Burke replied. However, insurance companies could "turn around and say they're not going to pay. There's nothing in the law about insurance companies following what FDA says."

"I've said it repeatedly, do not use the FDA label as the standard of care," Kessler said.

Lee Mortenson, executive director of the Assn. of Community Cancer Centers, said advocacy groups can

work together to get state legislation passed requiring insurers to reimburse for off-label uses.

FDA May Lack Resources To Review Anticipated New Cancer Drugs: NCI

FDA will be hard pressed to review the massive number of anticipated oncologic New Drug Applications in the next few years, an NCI executive told FDA officials last week.

Speaking at a meeting of cancer patient advocacy groups and FDA officials, NCI's Cancer Therapy Evaluation Program Director Michael Friedman currently is sponsoring more than 250 Investigational New Drug applications, 50 of which are potentially relevant to breast cancer.

"The challenge is formidable," Friedman said. In 1988, NCI filed 20 INDs; in 1991, NCI filed 31 INDs; in 1992, NCI filed 50 INDs.

NCI Resources 'Severely Tested'

"I'm not trying to suggest all agents will be effective, but we've never had so many," he said at the July 31 meeting. "The resources and staff of NCI are being severely tested, and if we succeed, the resources and staff of the FDA will be severely tested."

"How do we prepare ourselves at FDA to handle what's going to happen?" FDA Commissioner David Kessler asked.

"If we expect to have the volume of new agents approved that now are being tested, I don't see how FDA has the resources to deal with it," Friedman said.

As a result of the federal investment in basic research over the last 20 years, "huge volumes of new entities look very promising," he said.

"At NCI, we are feeling very stressed trying to study the new agents in a timely manner," Friedman continued. "FDA is going to be next. It's all going to be dumped on FDA. It should be a real concern."

No Cancer Letter For Two Weeks; Next Issue Scheduled For Sept. 4

The Cancer Letter will take its annual summer publishing break over the next two weeks. The next issue, Vol. 18 No. 34, will be published on Sept. 4.

The August issue of **Cancer Economics** will be mailed to subscribers near the end of the month.

The Cancer Letter office will be open, with Customer Service Manager Mitchell Harrison on hand to answer subscription questions at 202/543-7665; Editor Kirsten Goldberg will be available part of this time. The fax machine (202/543-6879) is always on duty.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. 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 NCI-CM-37821-12
RFP NCI-CM-37830-12
Title: In vivo testing
Deadline: Approximately Sept. 28

This is a clarification to RFP NCI-CM-37821-12 which appeared in the July 31 issue of **The Cancer Letter.** The following information was inadvertently left out: RFP NCI-CM-37821-12, In Vivo Testing, is an open competition. RFP NCI-CM-37830-12, In Vivo Testing, is a 100 percent small business set-aside. The standard industrial code is 8731. Offerors who qualify as a small business are encouraged to submit proposals under both RFPs. It is anticipated that a total of two incrementally funded cost reimbursement completion contracts will be awarded between these RFPs, with the contract period beginning on or about June 1, 1993. The contract period will be five years.
Contract specialist: Joyce Crooke
RCB Executive Plaza South Rm 603
301/496-8628

RFP NIH-ES-92-31
Title: Toxicity of lead in children trial: clinical center
Deadline: Approximately Nov. 4

The National Institute of Environmental Health Sciences seeks approximately three Clinical Centers for a clinical trial, the Toxicity of Lead in Children Trial. The objective of the trial is to test the use of the drug succimer in preventing lead-induced developmental delay. Children eligible for the trial will be about two years old and will be followed until they are at least four. The trial will be double blind to the extent possible. The target lead levels will be between about 20 ^g/dl to 45 ^g/dl. All children thought to be eligible will be treated for iron deficiency, be given vitamin and mineral supplementation, and have dust control measures instituted in their homes.

It is anticipated that there will be three Clinical Centers and one Coordinating Center.

Clinical Centers will cooperate with the Coordinating Center and the other two Clinical Centers in developing, testing, and refining the overall program and in writing the final protocol, Manual of Operations, and training materials before recruitment commences. Each Clinical Center will be responsible for screening, recruitment, randomization, treatment, developmental testing, and follow-up of study subjects. Optimally, no more than three Clinical Centers will randomize to drug or placebo on the order of 1000 total children during a 1-year enrollment and treatment phase.

The government estimates that an average of five professional FTEs, two technical FTEs, one clerical FTE, and one other FTE will be required on an annual basis per Clinical Center. The estimated period of performance is five years.

Requests for the RFP must reference RFP NIH-ES-92-31 and must be forwarded to:

National Institute of Environmental Health Sciences, Contracts and Procurement Management Branch, ATTN: Thomas Hardee, Contracting Officer, 79 T.W. Alexander Drive, 4401 Building, PO Box 12874, Research Triangle Park, NC 27709; phone 919/541-7893; fax 919/541-2712.

RFP NIH-ES-92-32
Title: Toxicity of lead in children trial: coordinating center
Deadline: Approximately Nov. 4

The National Institute of Environmental Health Sciences seeks a Coordinating Center for a clinical trial, the Toxicity of Lead in Children Trial (see above RFP). It is anticipated that there will be three Clinical Centers and one Coordinating Center. The Coordinating Center will cooperate with the three Clinical Centers in developing, testing, and refining the overall program and in writing the final protocol, Manual of Operations, and training materials before recruitment commences. The Coordinating Center will plan randomization of study subjects. Optimally, no more than three Clinical Centers will randomize to drug or placebo on the order of 1000 total children during a 1-year enrollment and treatment phase.

The government estimates that an average of five professional FTEs, two technical FTEs, one clerical FTE, and one other FTE will be required on an annual basis. The estimated period of performance is six years.

Requests for the RFP must reference RFP NIH-ES-92-32 and must be forwarded to: National Institute of Environmental Health Sciences, Contracts and Procurement Management Branch, ATTN: Thomas Hardee, Contracting Officer, 79 T.W. Alexander Drive, 4401 Building, PO Box 12874, Research Triangle Park, NC 27709; phone 919/541-7893; fax 919/541-2712.

RFAs Available

RFA CA-92-21
Title: **Transfer of new biostatistic methods to cancer epidemiology**
Letter of Intent Receipt Date: Sept. 30
Application Receipt Date: Nov. 12

NCI's Div. of Cancer Etiology announces the availability of an RFA to stimulate interest in small projects for the transfer of theoretical biostatistical methodologies to application in cancer epidemiologic studies.

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private. This RFA will use the NIH individual research grant (R01). The total project period may not exceed three years. The earliest anticipated date of award will be July 1, 1993. Approximately $500,000 in total costs will be committed for the first year. The intent is to fund 5 to 10 small research awards.

The purpose of this RFA is to stimulate collaborations and interactions among theoretical and applied biostatisticians, cancer epidemiologists, computer scientists, and programmers and to promote the introduction of appropriate theoretical methods to epidemiologic projects in cancer research. In many instances these grants will be small addenda to approved biostatistical and epidemiological R01 grants. This initiative proposes to link peer-approved activities to provide a mechanism for facilitating the transfer of new biostatistical methodologies to applied biostatisticians and epidemiologists. The goal is to ensure the validation and integration of promising new statistical and computing techniques into epidemiologic studies.

This RFA encourages the development of 5 to 10 small projects that will each provide enough support for one key researcher with expertise in the application of theory to real-life problems in cancer research, with appropriate collaborations. Subjects of interest include, but are not limited to:

- o Cox regression model
- o Logistic regression model, ordered logistic regression
- o Polychotomous regression model
- o Sequential trials; group sequential trials
- o Multiple endpoints
- o Surrogate endpoints
- o Time-dependent covariates
- o Censored data; left and right truncation
- o Meta-analysis
- o Data augmentation methods (Gibbs, bootstrap, and jackknife methods)
- o Martingales: counting processes in survival analysis
- o Frailties
- o Repeated measures
- o Determination of maximum tolerated dose
- o Surrogate markers of exposure

Inquiries may be directed to: Dr. Marthana Hjortland, Extramural Programs Branch, Epidemiology and Biostatistics Program, Div. of Cancer Etiology, NCI, 6130 Executive Boulevard, Executive Plaza North, Suite 535, Rockville, MD 20892; phone 301/496-9600.

Program Announcement

PA-92-95
Title: **Neuro-AIDS: HIV-I infection and the nervous system**
Application Receipt Dates: Sept. 1, Jan. 2, May 1

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH) invite research grant applications for support of research on neurological aspects of HIV infection (neuro-AIDS) in adults and children. Applications are solicited covering a broad range of activities in the neurological sciences from basic research to diagnosis and management of neurological complications including therapeutic investigations of HIV-related neurological disease in adults and children.

Research applications supporting the establishment or enlargement of collaborative and consultative neurologic units coordinated with AIDS Clinical Treatment Units (ACTUs) of the AIDS Clinical Treatment Group (ACTG), Women and Infants Transmission Study (WITS), and Multicenter AIDS Cohort Study (MACS) supported by the National Institute of Allergy and Infectious Diseases (NIAID) are especially solicited.

Applications may be submitted by foreign and domestic institutions, for-profit and non-profit organizations, public or private. This PA is intended to motivate individual scientists, inter-disciplinary research teams, and collaborative alliances to apply for research support to establish financially autonomous, but scientifically integrated, neuro-AIDS research nuclei particularly in partnership with ACTUs, MACS, and WITS.

Examples of research objectives appropriate for an application in response to this PA include:

--Studies of HIV-I infection of the CNS and subsequent neuro-AIDS complications in adults and children;

--Studies of AIDS-associated disorders of the PNS and resulting dysfunctions and abnormalities;

--Studies of the neurological complications of AIDS and its treatment and of opportunistic infections and malignancies;

--Studies of prevention, control, and treatment of opportunistic infections of the nervous system, such as progressive multifocal leukoencephalopathy cytomegalovirus toxoplasmosis, and fungal infections;

--Neuro-imaging studies of the manifestations of neuro-AIDS including positron emission tomography magnetic resonance imaging, magnetic resonance spectroscopy;

--Epidemiological studies of neuro-AIDS.

Direct inquiries to: Dr. A. P. Kerza-Kwiatecki, Program Administrator, Div. of Demyelinating, Atrophic, & Dementing Disorders, NINDS, Federal Bldg Rm 804, Bethesda, MD 20892; phone 301/496-1431; or Dr. Walter L. Goldschmidts, Office of AIDS Programs, NIMH, Parklawn Building, Room 15-99, 5600 Fishers Ln, Rockville, MD 20857; phone 301/443-7281.