THE CANCER LETTER

Vol. 15 No. 2

January 13, 1989

Price $185 Per Year North America
$200 Per Year Elsewhere

P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

President's Budget Asks $1.646 Billion For NCI In FY 1990, Including AIDS, 3% Increase Over '89

President Reagan's final budget includes an increase for NCI in the 1990 fiscal year of a little more than three percent over the current, 1989 fiscal year. The recommendations, which went to Congress this week, would leave the cancer program at close to current levels in most areas, with a budget of $1.646 billion, including AIDS money.

(Continued to page 2)

In Brief

Fishman La Jolla President Emeritus, Ruoslahti Succeeds Him; Ariz. Seeks Meyskins Replacement

WILLIAM FISHMAN, who with his wife, **Lillian**, founded the La Jolla Cancer Research Foundation 13 years ago, has assumed the position of president emeritus of the institution, which is recognized by NCI as a basic cancer research center. The new president is **Erkki Ruoslahti**, scientific director. Lillian Fishman is also giving up her various roles at the Foundation, including editing the monthly newsletter. The Fishmans will remain active with the Foundation without day to day responsibilities. . . . **UNIV. OF ARIZONA** Cancer Center is looking for a director of cancer prevention and control to replace Frank Meyskins, who is leaving to become director of the Univ. of California (Irvine) Cancer Center. The Arizona Cancer Center's cancer control program is recognized as one of the strongest in the country. CVs, two copies of recent publications, detailed description of research experience and goals, and three letters of recommendation should be sent to David S. Alberts, MD, Cancer Center Search Committee, Arizona Cancer Center, Rm 3945, UA College of Medicine, Tucson 85724. Deadline for applications is March 31. . . . **SOUTHERN ILLINOIS** Univ. School of Medicine is seeking a chief of its Div. of Oncology/Hematology, who will be associate professor or professor of medicine, depending on experience. Send resumes to Oliver Owen M.D., Chairman, Dept. of Internal Medicine, SIU School of Medicine, PO Box 19230, Springfield, IL 62794. . . . **CORRECTION**: Paulette Gray and Vincent Oliverio are members of NCI's Div. of Extramural Activities, not Div. of Cancer Etiology (**The Cancer Letter**, Dec. 9). Also, **John Niederhuber** is chairman of the Executive Committee of the American College of Surgeons Commission on Cancer, not of the Commission (**The Cancer Letter**, Dec. 9). Samuel Wells is chairman of the Commission.

President's Budget Would Leave Most NCI Programs At Same Levels As '89

(Continued from page 1)

The White House requested as it has in the past that all AIDS money allocated to the Dept. of Health & Human Services be administered from one office. Congress has rejected that request each time and probably will do so again. The total asked for AIDS spending by the department was $1.6 billion.

The Cancer Letter learned that the allocation to NIH of that amount would be $752 million, with NCI due to get $151 million. That would be an increase of $30 million over NCI's 1989 AIDS spending.

The total dollar increase for NCI over the current year would be approximately $75 million; thus, the increase allocated for cancer research and control would be $45 million.

The breakdown by funding mechanism in the 1990 NCI President's budget which was available this week did not include AIDS money. The figures which follow are somewhat less than the comparable amounts for 1989 for that reason, but when AIDS funds are factored in, they will in most cases be close to the 1989 figures:

Research project grants (ROs, PO1s)--$750 million.

Cancer centers--$97 million.

Clinical cooperative groups--$60 million.

Training--$33 million

Research contracts--$139 million.

Intramural--$254 million.

Prevention and control--$74 million.

Research management and support--$66 million.

Career awards--$8 million.

Clinical education--$2 million

Minority programs administered by the Div. of Research resources--$3 million.

All other--$8 million.

Not much would change in NCI funding patterns from the current year if the President's proposals remain intact:

*Funding of competing grants would remain at about the 21st percentile, although that is at best a guess now. NIH and NCI are still unsure of how the switch from priority scores to percentiles will impact funding levels, and in any case, it is too soon to estimate accurately numbers of approved grants and funds approved in review.

*The total number of grants, noncompeting and competing, would remain the same. However, there would be a few more in the competing pool in FY 1990 than there are this year, because more money will be freed up from the noncompeting pool with the expiration of more grants than there were last year.

*The percentage of reductions from peer review recommended levels would probably remain the same. NCI negotiated reductions averaging about two percent from noncompeting grants and 10 percent in competing grants this year.

Once again, there is no new money in the budget for construction. The Reagan budgets have consistently omitted construction funds. Congress has sometimes added money, but last year put in only $2.8 million for renovation and construction at the Frederick Cancer Research Facility.

The Research Facilities Branch in the Div. of Cancer Prevention & Control has been all but shut down. Its chief, Donald Fox, served several months last year and earlier this year as acting director of the division's Centers & Community Oncology Program, after Jerome Yates left. He resumed that role again after Robert Young departed.

The President did request startup funds for a new office building on the NIH campus.

The budget narrative states that at NIH, "basic biomedical research should be a priority," and the budget proposal "reflects the expressed scientific priorities of the biomedical research community. . . Basic research is a core federal function."

The document states that the budget will "stabilize and accelerate the accumulation of vital knowledge through a 6.6 percent increase over 1989 for basic research; commit $100 million in 1990 to the long term human genome project; and expand funding for biomedical research training by three percent."

THE CANCER LETTER

Editor: Jerry D. Boyd

Associate Editors:
Patricia Williams, Kirsten Boyd Goldberg

P.O. Box 2370, Reston VA 22090
Telephone (703) 620-4646

Published forty-eight times a year by The Cancer Letter, Inc., also publisher of The Clinical Cancer Letter and AIDS update.

Kennedy To Propose NIH Construction Authority Program Again This Year

Sen. Edward Kennedy (D-MA) is planning another attempt at legislation creating an NIH wide program to fund the construction and renovation of biomedical research and training facilities, a spokesman for the senator told **The Cancer Letter** last week.

The program, which Kennedy included in last year's biomedical research reauthorization, passed the Senate but was eliminated by House and Senate conferees upon opposition from the Administration.

The provision would have authorized $150 million in matching funds for the first year, and "such sums as may be necessary" for future years (**The Cancer Letter**, April 1, 1988). Kennedy is chairman of the Senate Labor & Human Resources Committee.

The Kennedy staff member said that details of this year's attempt have not been worked out, but indicated that the legislation would be similar to last year's.

An ad hoc panel created by NIH at the request of Congress last year to study biomedical research facility needs and develop recommendations for meeting them reported that from $2.5 to 3 billion over a seven year period is required to repair the infrastructure.

The Kennedy proposal last year did not change NCI's special authority to fund construction and renovation. The special panel's recommendation also left NCI's special authority intact.

The program would have required matching funds by grantees. The bill included a provision encouraging those awards to "emerging centers of excellence, which may lag behind in their institutional development or which have faced significant barriers to their development," Kennedy said last year at a hearing on the bill.

The Massachusetts senator also plans this year to introduce other pieces of legislation that would involve NIH, including:

--A bill incorporating some recommendations of the study conducted by the National Academy of Science Institute of Medicine on the NIH intramural program. That study was reported by IOM last month.

--A scientific misconduct bill.

--Legislation that would create a free-standing center for research on rehabilitation at NIH. A similar bill died in the last session.

After Congress met in joint session last week, Sen. Tom Harkin (D-IA) indicated that he will be the new chairman of the Senate Labor-HHS-Education Appropriations Subcommittee, replacing Sen. Lawton Chiles (D-FL), who retired last year.

Earlier indications were that Sen. Ernest (Fritz) Hollings (D-SC) would take the post, but according to committee staff members, he decided at the last minute to remain as chairman of the Commerce, Justice, State, the Judiciary and Related Agencies Appropriations Subcommittee. The post then went to Harkin as the next most senior Democrat on the subcommittee.

Harkin last year introduced in the Senate the bill creating a new NIH National Institute on Deafness & Other Communication Disorders.

Confirmation hearings for the President's Cabinet appointees are expected to begin late this month after Congress reconvenes Jan. 20. Louis Sullivan, President elect George Bush's choice for HHS secretary, is scheduled to appear before the Senate Finance Committee, which has responsibility for Social Security and Medicare legislation, including the Health Care Finance Administration which administers Medicare. That hearing will be held during the last week in January or early February, according to the committee's staff.

Sullivan will have a second hearing before the Labor & Human Resources Committee, which has responsibility for NIH authorization legislation.

While it is too early in the session to tell which items of legislation individual Congressmen plan to introduce, it appears that there may be a significant amount of legislation relating to AIDS research and AIDS patients.

A staff member for Sen. Barbara Mikulski (D-MD) a member of the Labor & Human Resources Committee, said Mikulski's health agenda will emphasize antidiscrimination legislation for persons with the AIDS virus. Any new appropriations for those proposals would focus on the Americans with Disabilities Act, the staff member said.

Other Mikulski proposals may include the expansion of Medicare coverage for preventative cancer care and encouraging FDA to expedite approval of cancer and AIDS drugs.

On the House side, a spokesman for the House Subcommittee on Health & the Environment, chaired by Rep. Henry Waxman (D-CA), said he did not expect any legislation

involving NCI to come up this year.

Early next year, he said, there may be another attempt at providing incentives for top government scientists to remain on the job, one of the most vexing problems facing the biomedical research community and NIH.

The establishment of a Senior Biomedical Research Service, which Kennedy proposed to permit pay increases of 10-15 percent over civil service and Public Health Service levels, was eliminated from the final bill.

Last November, President Reagan signed the Health Omnibus Extension Act of 1988, which reauthorized various biomedical research activities, including the National Cancer Act. It was a two year renewal, so a reauthorization bill will have to be approved by September 1990. Some NCI advisors and constituents, already starting to draw up amendments for the next round, have said they are hoping for a five year renewal.

FDA Drug Approval On Activity Versus Survival Urged By NCI

FDA should approve new cancer drugs on the basis of activity rather than survival, Div. of Cancer Treatment Director Bruce Chabner told the first meeting of the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS.

Chabner suggested that FDA accept a single criterion of efficacy, such as "the ability to produce consistent antitumor responses or meaningful improvements in quality of life," without requiring comparison with standard therapies. Noting that the agency is not satisfied by a demonstration of antitumor activity, he said FDA instead seeks evidence "of equal or greater survival with a new drug before granting NDA approval."

The meeting was held under the auspices of the President's Cancer Panel, which was requested to conduct a review of the drug approval process for cancer and AIDS drugs by Vice President George Bush last year.

Chabner cited FDA's failure to approve the cisplatin analog carboplatin for first line treatment of advanced stage ovarian cancer. Although clinical trials have demonstrated equal response rates and less renal toxicity with carboplatin than cisplatin, "FDA wishes to see equivalent or better survival" and is therefore unlikely to approve the agent for first line use until 1991 or 1992.

NCI believes "that the demonstration of consistent complete responses in any type of cancer should be sufficient evidence for drug approval, and that the demonstration of partial or complete responses in a significant fraction (perhaps 20 percent) of patients with stages or types of cancer refractory to standard therapy should be sufficient for approval," he said. "We do not feel that survival equivalence or superiority should be required as part of NDA approval, because this criterion only delays the broadening of clinical experience with active new agents."

FDA Office of Drug Research & Review Director Robert Temple explained the agency's action on carboplatin to the committee.

"The conclusions for advanced ovarian cancer was that a better survival rate than could be achieved with current therapy would an adequate basis for approval."

The FDA advisory committee "felt that if survival rates were equivalent under the circumstances of ovarian cancer, there should be some survival data. The reasoning was that this is a tumor that can be cured in a fraction of cases and where the current treatment has clearcut and rather large effects on survival. They concluded that equivalence of response rate did not necessarily translate to equivalence of survival."

In addition to the issue of using endpoints other than survival to approve cancer drugs, NIH officials also called for more flexibility in modifying protocols approved by FDA, and an examination of what they characterized as outdated requirements for animal toxicology studies, particularly for biologics and natural products.

Committee member Peter Hutt, formerly general counsel for FDA, asked Chabner to rank the following problems in NDA approval for cancer and AIDS drugs: endpoints (activity versus survival); physiologic action versus clinical benefit; and the need for two studies.

"The question of endpoints is the most important one," Chabner said. "If we could reach agreement, I think a change in philosophy about what constitutes efficacy could be made. I think that would be a very significant step."

Discussing physiologic action versus survival or other longterm clinical benefit, Chabner said he believed FDA is currently grappling with the issue. "I am concerned about the delay in approval for erythropoietin," he said. "It's an important issue because it's a prototype for how these biologicals are going to be handled."

Chabner also expressed concern about the

cost and delays due to FDA's frequent insistence on two studies for drug approval.

"For example, with flutamide, when it was presented for consideration, we went through this strange gyration of having to break one trial into two parts to try to get at whether we could satisfy the requirement." Although "I think they make exceptions," such as approving ifosfamide for third line therapy of testicular cancer, FDA "usually stands by" the requirement for first line therapy.

Hutt also questioned Chabner about his assertion that no supplemental NDA should be required for a new indication for an already approved drug, asking what mechanism could be used instead.

Chabner suggested that FDA establish an advisory body to decide whether to extend a drug's indication. "Once we know that a drug is safe in terms of clinical practice and it has effectiveness in one disease, I think extension to other malignancies should not require extensive review by FDA."

Hutt, however, said it could be problematic to allow such an extension for cancer drugs, but not other drugs, such as antibiotics.

"The issue is much easier to show in many other situations," NCI Director Samuel Broder said. "That's one of the most difficult concepts to get across. If you're an oncologist, you revere the concept of a complete clinical response" in an advanced malignancy. "It is not a common event. It is something that is cause for immediate reaction," he said. "So what we get into is a situation where people realize that a drug is working, and feel compelled to use it, their patients demand access to the drug, and we have a number of barriers for their implementation.

"I hope one of the things that you can focus on...is the issue of survival as an endpoint, because to me that is one of the most significant impediments for us to apply technology." Whereas oncologists "will stand up and salute" a report of a complete response in advanced colorectal cancer, FDA will say, "well, but show us your survival data."

Chabner asserted that NDA approval is the most important issue facing NCI in the drug approval process, "and getting some agreement that we don't have to show survival advantages in randomized trials to get NDA approval."

DCT's Board of Scientific Counselors prepared a series of recommendations to FDA on approval of new cancer drugs last February, but as yet, has received no formal response from the agency. FDA Center for Drug Evaluation & Research & Review Head Carl Peck, however, told the board in June that he was in "essential agreement" with the recommendations, Chabner said.

Hutt repeatedly suggested that the issue of endpoints for approval was one that could be resolved by regular luncheon meetings between Broder and his counterparts at FDA.

"No, we could not resolve it," Broder said. "This is an area where there are strongly held philosophical views.

"We have two worlds here--we're operating under different assumptions. I don't believe that the FDA recognizes and accepts complete response rates as an indication for approving a drug and therefore we are caught in the trap of having to do survival data, which in effect, is another way of denying access to that drug."

Problem Complicated By Off Label Use

The problem is further complicated by "a new nuance that is attached to FDA approval" of a drug, in which third parties refuse to pay for off label uses of drugs.

When Hutt again suggested that luncheon meetings could address such issues, Broder said, "This is a societal value, it is not an administrative value among agencies.

"We have to impress upon the FDA what's applicable. Requiring survival in 1950 or early 1960 might well have been a logical thing to do because as a practical matter, very few things worked, and there was so much of a possibility for abuse or commercial exploitation...I really don't think it is appropriate to frame it as an arcane administrative thing."

During his testimony, FDA Commissioner Frank Young asserted, "It is absolutely a myth that survival is a requirement by FDA" to approve a cancer drug. He added, however, that investigators and FDA need to agree on endpoints "upfront."

Hutt asked Young about his definition of phase 2 under FDA's new guidelines for approving drugs at the end of phase 2 for life threatening illnesses.

"I think that in some cases, there may be randomized trials, but I think in the larger number of cases, when we're dealing with therapies that are already in existence, it would be just as" with AZT. "If you have a proven drug for that particular disease, then you do your control against that drug. We have also done historical controls, we've done

drug to drug controls, we've done open protocols."

Hutt asked if the critical stage would be "the end of phase 1 conference at which FDA and NCI would agree upon the protocol, i.e., as to whether it would have to be randomized or not?"

"That's correct," Young said. "I would reject out of hand the fact that FDA requires in every case a randomized protocol."

Chabner, however, said, "at the end of phase 1, we often don't have information about activity in specific diseases. It's only when we get into phase 2 that we begin to identify activity and response rates, and then we enlarge on that trial, maybe do several trials in a specific disease and find that we have a reproducible response rate of 20, 30, 40 percent.

"What I'm talking about is after that response rate is identified, not requiring a randomized comparison with other single agents. If you really go into that kind of phase 3 study, you're going to prolong the approval process for a number of years. I think a good example of this is the carboplatin story...I don't think there's anyone that would argue that carboplatin does not have a equal response rate to cisplatin, and a definable and reproducible response rate in ovarian cancer, and yet the requirement for getting an NDA for first line use for carboplatin now is to demonstrate in combination therapy equal survival to the cisplatin combination in a randomized trial. That's what I'm saying I don't think should be required."

Young acknowledged that investigators may not have all necessary information available at the end of a phase 1 trial. "But if you consult with FDA early, and during the trials, we can provide...the kind of information on how the evaluation is going to be made, and that's the exact heart of the proposal. I think the agency and NCI are at a disadvantage if one comes in with a study already done and then says 'can this fit the criteria?'"

"I think in this instance, there's a more basic disagreement about what is an acceptable endpoint," Chabner said. "Do we have to demonstrate equivalence of survival in a randomized phase 3, or is phase 2 activity sufficient?"

Young suggested working groups get together in order to discuss the issue.

Asking if there is "any kind of standing liaison" between NCI and FDA, Hutt said he was hearing "massive miscommunication, and massive misunderstanding" between the two institutions.

"I don't think that is the issue at all," Broder said. "I think we are missing some global concepts. The global concepts that we need some help on are when do we make a drug available--available in a real sense, not a theoretical sense."

In cancer, for example, NCI believes that complete response rates in advanced malignancies "define that a drug should be available" through prescription. "The FDA does not agree with that."

"We've tried," Chabner said. "I don't think it's fair to say we haven't." DCT has invited FDA to three BSC meetings, "and we still haven't gotten an answer."

Young cited correspondence between Peck and Broder as a pledge "to reestablish connections. I thought a few years ago the connections were quite good down at the working level, but for reasons that I don't understand completely, there seemed to be some deterioration about a year and a half ago."

Young suggested "vigorous and interactive debates on what endpoints should be." He also suggested that "as trials are being developed, we should have individuals discuss the protocol with FDA. The whole idea of the vice president's initiative is to get it right the first time. As we reviewed some of the clinical trials, I was appalled at the surprisingly large number of trials that were flawed, and that information was not able to be gained from, and I think that should be avoided." Young again suggested a "problem oriented" working group that would identify problems in the approval process, as well as conduct a retrospective analysis of past approvals in order to identify where changes could be made.

During the lunch break of the meeting, FDA's Peck and Chabner met and discussed monthly meetings with relevant staff from each agency.

Flexibility To Modify Protocols Urged

Another issue raised at the meeting concerned investigators' flexibility to modify protocols in phase 1 trials.

Chabner reported that the initial IND process works fairly well, particularly for chemotherapeutic agents. NCI, however, frequently encounters disagreements with FDA about changes in protocols.

"There have been major disagreements, for example, with the IL-2/LAK study and TIL studies, with DDC and DDI in the pediatric

AIDS population. Once a phase 1 trial has begun and we begin to accumulate information, we don't feel we have the flexibility to make changes in the protocol."

For AIDS drugs, "the major problem we've had with the initial protocol has been in issuing pediatric protocols and then in revision of any of these protocols during the initial trials," he said.

"We've encountered problems particularly in making changes with regard to duration of therapies, multiple cycles of therapy, changes of schedule and administration, and the desire to early implement studies in pediatric populations."

Proposals To Deregulate Phase 1

Hutt asked Chabner about proposals to deregulate phase 1 and allow investigators to conduct phase 1 trials after approval by an institutional review board rather than FDA. "From what you describe, that would not improve the system very much."

"It could," Chabner said. "I would say in one regard we've had some problems in terms of the initial protocol in that in general, they're more conservative than we are. For example, we would like to switch from i.v. to oral medications for the AIDS drugs more quickly than they would allow us. They want to see the i.v. results first, before they would allow that switch to take place.

"The duration of therapy and multiple cycles of therapy has also been a problem. For example, IL-2/LAK, we were restricted to one cycle of therapy. Initially we wanted to repeat that, but they wanted to see the results first from that initial cycle of therapy. There are some issues with regard to initial protocols, they haven't prevented us from (conducting) the studies, but we would like greater flexibility in the beginning."

National Institute of Allergy & Infectious Diseases Director Anthony Fauci also cited the need for more flexibility in modifying INDs.

Hutt, however, said, "It is my understanding that you can proceed to modify your protocols by simply informing FDA without ever getting their approval, yet you say that they won't give their approval."

"We don't like to do that," Chabner said. "We don't like to submit a protocol, and then receive negative comments, and then go ahead in spite of what they say. We feel it places us on dangerous ground, and in general, we don't do that."

"What you're describing then is not a problem of the regulations, but a problem practically created by your own practice," Hutt said.

"The technical statement that one technically under a literal interpretation of a statute, might be able to do something, wouldn't be helpful to us," Broder said. "We need to have a more substantive working understanding than that. We need to have some sort of policy guidance. I cannot conceive of a situation in which the FDA admonished us not to do something that we would proceed. We might argue, we might take it to the public, we might ask for your intervention, but we would not proceed until that admonition was lifted."

"Once an IND is approved, anyone," Hutt said, "can proceed to modify the IND after changes have been submitted to FDA."

Broder, however, said that "sometimes in order to get a study moving, we will have an understanding that we will proceed up to a certain point...We sometimes have to concede that we will come back and we will not proceed beyond a certain point without their input."

Sometimes "we get into protracted discussions, time consuming discussions, delaying discussions, over which laboratory tests will be used, on tests that have no bearing on the primary issue of a phase 1 study." Other discussions include the oral bioavailability of a drug, or, in the case of IL-2/LAK therapy, the insistence by FDA that therapy must be stopped even though it has induced clinical responses in patients for which no other modality has been successful or is available.

"We feel that there is an excessive attention, micromanagerial (attention) as to how to do things."

NCI and FDA also have strong differences in opinion over when to proceed with clinical trials in children with AIDS, he said.

"In the pediatric setting, we can be in a setting where we have strong disagreements about when one will take a new agent into children, and we are in a situation like that now where there is a disagreement as to whether a drug can be used in children under two," he said.

"I really believe that it is not appropriate to frame that as some sort of technical disagreement. I will say that we will not proceed if the FDA tells us not to give this drug to children under the age of two, we will not do it. But I think it is wrong to proscribe us from doing that."

"Is this a situation of purely technical detail where two scientists disagree?" Hutt asked.

"We are the people that are dealing with patients, we are the scientists that have developed the products, and we should be given some credit for having a sense as to where to go with new protocols and some leniency rather than being micromanaged," Chabner said.

"We believe that for a child under the age of two with HIV infection, the child will die, and therefore we have a certain urgency about how we approach the problem," Broder said. "We believe that there are options available, there is AZT to some extent, but AZT has both its good points and its limitations and there's a lot that really AZT cannot accomplish. We feel that there are preliminary data from adults" that warrant pediatric trials of new agents, he said.

"For example, we are in a situation now, where the argument, at least one argument for not moving with an agent in a child, is that we have failed to show toxicity in an adult" with the agent dideoxyidenosine. "Try explaining that to a parent."

Chabner then asked Hutt, "So what you're saying is that you feel we should just ignore what FDA says?"

Hutt said it depended on whether FDA formally disapproves a revision or simply states that it prefers it not be done. "One you can ignore, the other you can't."

""We don't ignore what the FDA says," Chabner replied.

"I understand," Hutt answered. "You asked me a legal question, I gave you a legal answer."

"That's the functional equivalent of saying 'do I have a common law right not to respond to a policeman when he asks you to stop,'" Broder said. "You might in fact under the common law, be permitted to deny what a policeman is asking you to do, but it is usually unwise." The same problem "can be addressed by asking the police department to modify its regulations and operating procedures."

"I sense the following contradiction in what you're saying," Committee Chairman Louis Lasagna said. "On the one hand, you're saying, 'we ought to be free to make changes in protocols, we're smarter than the FDA...then you say, 'but, we want their approval.'"

"We need their approval," Chabner said. "I don't want their approval. I would rather they didn't exist.

"The fact that they do exist means that I need their approval...If I were to proceed with doing studies that they said I shouldn't be doing as a routine, I think I would be placing the whole experimental drug development program in great jeopardy. The first time we had an unfortunate side effect, I would be paying for it," he said.

"I think it's unfair to characterize this as a confrontation between the NCI and FDA. It's a confrontation between FDA and the community of people who produce cancer drugs, and that includes pharmaceutical companies and academic centers as well as NCI."

In questioning Young, Hutt acknowledged FDA's concern that investigators may go down the wrong route in conducting clinical trials, but pointed out that FDA IND regulations say the agency will stay out of non safety issues in the phase 1 IND. In spite of the regulations, however, FDA routinely makes nonsafety observations.

Young answered that he viewed the situation as one of "Pay me now or pay me later." Safety "is the overriding issue," he said, adding that FDA believes it "can be of help.

"If an individual investigator wishes to go down a route that is less than productive in our eyes, we will give...our best advice," he said. "One of the things that I see is very difficult...is that we've seen (trials in which) the endpoints change, the outcomes are different" and the NDA needs to be "resuscitated."

FDA "can provide in our opinion the best advice...We have to hammer out the honest differences on protocols, and if the end of day comes, and the individual wants to go ahead and it is safe...FDA should not stop him, even though it may led to folly. We have to document our concern."

Chabner also raised the issue of what he characterized as outdated requirements for animal toxicology, particularly for biologics and natural products.

NCI and FDA currently have a memorandum of understanding to deal with standard chemotherapeutic drugs.

"I think the major problem for toxicology is in the area of biologics, where animal toxicity is not always useful because of this problem of cross species reactivity or lack of activity."

Chabner said Young has publicly questioned whether the old approach to toxicology is applicable to biologics and natural products. "I think a change could be implemented simply by a change in policy of the FDA."