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Phase 0 Trials Signal FDA's New Reliance On Biomarkers In Drug Development

By Paul Goldberg

FDA earlier this week announced regulatory measures that make it easier for drug developers to begin early testing of compounds in people.

In a guidance to industry, FDA established a new category of "exploratory studies" that may help select compounds for development before phase I dose-escalation trials, and, in a related rule, the agency waived the "good manufacturing practice" standards for compounds that can be used in early-stage clinical research.

The rule, which was published in the Federal Register, makes it possible for academic research laboratories and drug companies to generate phase I compounds without having to meet the same requirements as drugs and biologics that have gained marketing approval or are being tested in phase II and phase III trials.

Experts in early-stage clinical trials said the new rules may be a step in the right direction, albeit one that poses logistical and scientific problems, which may begin with the difficulty of convincing subjects to take part in

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NCI Budget:

NCI Faces $32 Million Reduction In FY 2006; NIH Plans 2.35% Cut In Grant Budgets

By Kirsten Boyd Goldberg

The NCI budget for fiscal 2006 will be $32 million less than the institute's budget for the previous year under the appropriations bill for fiscal 2006 that President Bush signed Dec. 30.

The bill included $28.6 billion for NIH and $4.842 billion for NCI. However, a 1 percent across-the-board reduction will cut those amounts by $286 million for NIH and $48 million for NCI.

The revised NCI budget is $4.793 billion.

Under a grant funding policy issued earlier this week, NIH plans to award 97.65 percent—i.e., cut 2.35 percent—from the FY 2006 budgets of non-competing awards. Also, the grant budgets for future years would be cut by the same amount.

NIH plans to restore funding of up to 97.65 percent to grantees who didn't receive full funding yet this year. Some awards were reduced while NIH awaited Congressional action on the appropriations bills.

NIH said competing grants "will be managed to an average award

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Agency Eases Requirements For Making Phase I Agents

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clinical research that has less of a therapeutic potential than current phase I trials. Also, usefulness of data from exploratory studies would be limited, especially in cases where therapeutic value of drugs is dependent on administration of the optimal dose, experts said.

At a press conference Jan. 12, FDA Acting Commissioner and NCI Director Andrew von Eschenbach described the changes as a an effort "to bring all of the fruits of scientific discovery to the point where they are actually impacting on people's lives, and improving those lives, and saving those lives."

Von Eschenbach said the agency's goal is to increase the number of drugs that get through clinical trials. "Consider just one stark statistic: Today, nine out of 10 compounds developed in the lab fail in human studies," von Eschenbach said. "They fail, in large part because they behave differently in people than they did in animal or laboratory tests."

Though press conference materials identified von Eschenbach by his FDA title, he could just as well have spoken in his NCI capacity, since the proposals stem from deliberations of a "task force" formed by the two entities.

In his remarks, von Eschenbach didn't mention his goal to "eliminate suffering and death due to cancer" by the year 2015, which he has said guides his programs both at the research institute and at the regulatory agency. Nonetheless, the new measures appear to represent the first move by FDA Acting Commissioner von Eschenbach to implement the programs developed under NCI Director von Eschenbach.

Phase 0 Trials Not Limited To Microdoses

The concept of exploratory trials, also known as phase 0 trials, has been discussed at FDA and in the academia for about three years, sources said.

To institute this approach, the agency needed only to publish a guidance document, said Janet Woodcock, FDA deputy commissioner for operations. "The exploratory IND is within the FDA's current regulatory framework," Woodcock said at the press conference. "It does not require any change in regulation or our approach. It simply explains to researchers how they can take advantage of the inherent flexibility in the current regulation."

Discussion at the press conference was focused on using exploratory agents in "microdoses," defined as less than 100th of the amount of the drug calculated to yield pharmacologic effect.

However, the guidance doesn't impose such limits on investigators. The document states that physicians can also work with doses that "produce a pharmacologic, but not toxic, effect." Studies could be conducted either in patients or in healthy volunteers, and administration of the agents can be repeated.

Also, according to the document, a single filing could be made for several closely related agents, and agents that clear phase 0 could be advanced to phase I trials, which seek to define the human dose.

In exploratory trials, "you might have a smaller number of animal species than you usually have—just one animal species rather than two animal species—and you might not have to test animals as extensively with as high a dose that you did, but you would still have to do some testing in laboratory animals to ensure that the dosage that you then give people are safe," Woodcock said.

The text of the guidance is posted at www.fda.gov/cder/guidance/7086fnl.htm.

The agency's move to create phase 0 trials is closely related to its decision to waive current good manufacturing practice requirements for agents entering phase I testing.

"The problem was that GMP regs had a one-size-fits-all approach to manufacturing," Woodcock said. "You had the same requirements for huge plants making millions of doses, and the same requirements for production of very tiny doses for initial human use.

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The regulations were written with these factories in mind, and didn't fit laboratory production. [The new rule] allowed FDA for the first time to give direction and advice to researchers on how to safely produce small quantities of compound in the laboratory that then can be used in people."

In its "direct final rule," the agency states that the regulations that govern INDs give it sufficient authority to oversee trials.

"The Commissioner is considering proposing additional CGMP regulations to cover drugs in research stages," the rule states. According to the document, these regs would "clarify the agency's expectations with regard to fulfilling CGMP requirements when producing investigational drugs for phase II and phase III clinical studies."

The new rule is posted at www.fda.gov/cder/guidance/6164dft.htm.

The agency's decision to waive manufacturing regulations would be useful to academics, Woodcock said. "This will be especially valuable for academic and NIH researchers in medical schools, who have many discoveries, but don't have large factories and facilities at their disposal," she said.

Steven Rosenberg, chief of the NCI surgery branch and its tumor immunology section, agreed that the waiver would benefit researchers.

"The requirements made it extraordinarily difficult for medical scientists like me to bring drugs to patients," said Rosenberg, a member of the NCI-FDA panel that proposed the changes. "We've been at the mercy of large biotech and pharmaceutical companies who have the resources to fulfill the very stringent regulations that exist for taking these new products to very large numbers of patients."

The final rule estimates that the reduced documentation burden would save pharmaceutical companies $1,440 per IND application. Chemical companies that choose to make use of the new rules may have to develop new control procedures, which would increase their costs by $810 per IND.

Woodcock said practices at pharmaceutical companies would be unlikely to change.

"We expect most pharmaceutical and biotech companies will be manufacturing the product the way they usually do, because that's the way they do things," she said.

Selection Based on Biomarkers

Anna Barker, NCI deputy director for advanced technologies and strategic partnerships, acknowledged that academics would be more likely than drug companies to use the new mechanisms.

"This is a paradigm shift for investigators working in the academic labs as well as ultimately what will happen in the commercial sector as a consequence of this," she said at the press conference.

"We believe that the combination of the exploratory IND and its use will significantly streamline the drug development process, not just for cancer, but for all diseases," Barker said. "The realization of molecular oncology depends on this kind of progress."

Through most of his four-years at NCI, von Eschenbach advocated greater reliance on biomarkers in drug development. Though few biomarkers have been validated clinically, scientists routinely rely on such measurements in early development of drugs, in essence making educated guesses.

"The way we are functioning now, we take a drug out of a laboratory or out of animals, and then we have to go into full-blown clinical testing, exposing large number of patients to escalating doses in order to figure out what works and what should go on to commercialization and mass scale-up," von Eschenbach said.

The new regulations unabashedly place determinations based on biomarkers squarely at the earliest stage of clinical research and the drug approval process, observers said.

"[The new approach] enables us to make rational, intelligent selection of drugs in a way that not only predicts their efficacy, but does it in a way that minimizes the risk of finding this out in the first place," von Eschenbach said.

In addition to accelerating discovery of new compounds, the changes would allow researchers to re-evaluate the potential of existing drugs and biologics, Barker said.

"We are going to have an opportunity to begin to look at existing drugs in new ways and ask new questions, both in other diseases and analogs of drugs that may be in the clinic already," said Barker. "I think it opens up an enormous range of opportunities, including new targeted therapies."

To make use of the new regulations, the NCI intramural program has set up "a special new unit to do these types of trials on promising candidate drugs," said James Doroshow, director of NCI's Division of Cancer Treatment and Diagnosis.

"It is now vital that cancer researchers in academia and the private sector take full advantage of these new opportunities to perform these types of exploratory studies," Doroshow said in a statement.

Phase 0 Raises Questions

Outside NCI, academics viewed the new regulatory approach with caution.

"It will be a very useful thing for imaging people," said Bruce Chabner, chief of hematology and oncology at Massachusetts General Hospital and an expert in drug development. "It could give you important early clues. They will be able to look at compound distribution, or uptake, or receptor-binding." Typically, imaging studies can be performed using microdoses of compounds.

"The problem is that with drugs that you use at small doses, you don't always get an accurate picture of what happens to an actual dose that you give to a patient," Chabner said in an interview. "The doses we would be studying would be far from doses you will end up using to treat patients, and many drugs have very dose-dependent features. If you don't give the right amount, you don't saturate metabolic pathways. Absorption studies can be erratic at low doses. The question is how reliable it will be for an average drug."

Chabner characterized the change as "a step forward," albeit one that will not significantly change the success-to-failure ratio in development of cancer drugs. "I doubt that this is going to improve that ratio so that five out of 10 drugs make it," he said.

Exploratory studies would be more feasible at microdoses in healthy volunteers than in cancer patients, said Mace Rothenberg, Ingram Professor of Cancer Research at Vanderbilt-Ingram Cancer Center.

"As altruistic as cancer patients are, I don't think that they would embrace the idea of microdose studies that have virtually no chance of helping them," he said. "Also, there is a presumption here that we know the target, and that we can extrapolate microdose pharmacokinetics to real dose pharmacokinetics. Neither of those assumptions may be correct."

The agency's decisions to allow exploratory trials, while easing the requirements for production of agents, is a "double-edged sword," Rothenberg said.

"On the good side, it will allow new agents to enter human testing more quickly than before," he said. "There will be fewer arbitrary delays based on GMP considerations, for instance. On the bad side, these trials will likely include only one cycle of therapy (since supplies of the drug will be very limited), so patients who benefit may not be able to continue on the drug. In addition, with the need for testing in only one species of animal, we will observe new, and maybe unexpected toxicities during the initial small clinical experience.

Rothenberg said the changes raise questions that physicians will have to address with their patients:

"What kind of a trial is it? Is it a phase 0 or phase I? Is it a microdose or is it a higher dose? Is it one cycle only? Is it going to be continued treatment until disease progression? Is it going to be biomarker-driven, in which case, if you biomarker doesn't act in the right way the treatment is stopped? Or are you going to be selected based on biomarkers?"

NCI Budget:

NCI Official Urges Staff To Study Institute Priorities

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amount equal to FY 2005 levels." The policy provides a 3 percent "escalation factor in the amounts indicated for future years on competing RPG awards which are not based on modular applications."

Policies for other grant programs will be established by each institute, NIH said.

"Over the past few years, we have become accustomed to adjusting to budget constraints and the current year is no different," NCI Chief Operating Officer John Niederhuber wrote in a message to the institute's staff. "It remains critical that we continue to engage in careful planning, monitoring, and reporting of progress made towards NCI's challenge goal to eliminate the suffering and death due to cancer. NCI's Strategic Priorities are a clear signal of where we will be focusing our valuable resources in the year ahead and beyond."

The institute's list of strategic priorities has been completed and will be made available soon, Niederhuber wrote. "I strongly urge you to study our priorities so that you can better communicate them to the community," he wrote to the NCI staff.

"We need to deliver a rational, clear message that assures confidence in our fiscal management," Niederhuber wrote. "NCI must and will continue to be the driving force for innovative cancer research, from discovery and development to delivery."

Earlier this week, NCI officials discussed the budget at a "Joint Board Retreat"—a meeting closed to the public—with members of the National Cancer Advisory Board, the Board of Scientific Advisors, and the Board of Scientific Counselors. The institute expects that its operating budget will drop in FY 2007 as well, sources who attended the meeting said.

NCI advisors appeared to favor funding more grants for less money per grant than providing full funding for fewer grants, sources said. Also, the advisors urged the institute to protect funds for new investigators.

NCI Issues P01 Guidelines

In another development, NCI issued new guidelines for Program Project (P01) grants, which include changes in the review and scoring process, and policies for amended applications.

Beginning with applications submitted for the February 1, 2006, receipt date:

—All NCI P01 applications will be reviewed in large (up to 10 applications) clusters.

—Applications will be reviewed by Special Emphasis Panels which will include members of the NCI P01 Parent Committees and other appropriate reviewers.

—The SEP will discuss and score projects, cores, and the overall program, and assign the final priority score for each application.

—The SEP will have the option to streamline the review and unscore applications with low merit.

—Telephone conferences with applicants during the review will be discontinued.

—Program leadership will be reviewed under Overall Program Investigators.

—Integration will be reviewed as part of the Overall Program.

Changes in NCI P01 policies regarding amended applications:

—Amended P01 applications which have had one or more projects funded since the previous submission must have at least two unfunded projects in order to qualify for submission of the P01.

—The already funded project(s) will not be discussed or scored separately during the review of the P01 application; they will be considered under the Environment and Integration review criteria for the Overall Program.

—If the P01 is to be awarded, already funded projects will be folded into the P01 at the awarded budget levels and for the remaining awarded years of support.

—Accelerated peer review of amended applications has been discontinued.

The guidelines are available at http://deainfo.nci.nih.gov/awards/P01.htm.

* * *

THOMAS HOOVEN has been named NCI Deputy Director for Management. Hooven was previously the associate director for administration at the National Institute of Child Health and Human Development for six years. He worked in a variety of positions at NCI over seven years, including budget analyst, administrative officer, and management analyst.

Obituaries:

Howard E. Skipper, Pioneer Of Cancer Drug Development

By Kirsten Boyd Goldberg

Howard Earle Skipper, a pioneer in cancer research who established and led the cancer drug research program at Southern Research Institute for more than 40 years, died Jan. 2. He was 90.

Skipper demonstrated that combination chemotherapy could eliminate cancer cells in animal models. His 1964 paper describing the inverse relationship between the amount of cancer in the body and its curability is considered a classic, according to "The Cure of Childhood Leukemia," by John Laszlo (Rutgers University Press, 1996).

During his tenure at Southern Research, the institute's scientists designed and developed four commercial drugs and more than a dozen clinically evaluated drugs.

"Dr. Skipper led the way for all of us here at Southern Research Institute, as well as for many cancer researchers and clinicians all over the world, in the search for new drugs to combat cancer and new approaches to treating cancer," said John Secrist III, vice president of drug discovery at Southern Research. "He inspired us to think about cancer in new ways, and in many ways served as a mentor for us, even to this day."

Skipper, born in Sebring, Fla., won a football scholarship to University of Florida at Gainesville, where he earned a B.S. in 1938, an M.S. in 1939, and a Ph.D. in 1941 in biochemistry and nutrition. Drafted two weeks after receiving his doctorate, he served in the Army Chemical Warfare Service for five years during World War II. He received an Army Commendation Citation Medal and retired with the rank of Lieutenant Colonel.

Skipper joined Southern Research in 1946, where he advanced from assistant director in 1949 to vice president in 1964. He and his colleagues established a number of principles based on analysis of experiments with leukemia in mice, which proved valuable in planning strategies for cancer treatment.

"Howard Skipper, in collaboration with the late Frank Schable, pioneered the development of animal models which formed the basis for the development of curative combination chemotherapies for leukemia, lymphoma, and other malignancies in patients," said Emil Freireich, director of special medical education programs at M.D. Anderson Cancer Center.

Skipper wrote extensively on the effects of

various drugs and treatment schedules on the growth, regression, and re-growth of tumors, and introduced the concept that all cancer cells must be killed to ensure the survival of the patient. He made major contributions to studies involving a variety of regimens using several drugs in combination to avoid the occurrence of drug resistance or to minimize the drugs' toxic effects. He also conducted studies on the use of drug treatment following surgery or radiation therapy.

In 1974, Skipper was named president of Southern Research Institute, but also remained director of its Kettering-Meyer Laboratory. He retired in 1981, and a research building—the Howard E. Skipper Chemotherapy Laboratory—was named in his honor. He continued his research full-time until 1989.

Skipper served on numerous councils, committees and boards of cancer and scientific organizations, including the Presidentially-appointed National Cancer Advisory Board from 1972-1977. He received many awards, including the Bristol-Myers Award for Distinguished Achievement in Cancer Research, the Albert Lasker Basic Medical Research Award, the American Cancer Society Award for Distinguished Service in Cancer Control, the Charles F. Kettering Prize, and the American Cancer Society National Award.

Skipper was preceded in death by his wife, Margaret Edwards Skipper. He is survived by a daughter, Margaret Ann Skipper, and a son, Howard Earl Skipper Jr., both of Birmingham, Ala.

John R. Murren, Lung Cancer Specialist

John Robert Murren, 47, chief of the Yale Medical Oncology Outpatient Clinic and director of the Lung Cancer Unit at the Yale Cancer Center, and a founder of the Nevada Cancer Institute, died Dec. 28 at NIH in Bethesda, Md. He had melanoma.

Murren had the largest clinical practice at the Yale Cancer Center, but also was known for his clinical research on drug therapies. He served on the Clinical Research Subcommittee of the American Association of Cancer Research and the American College of Surgeons Cancer Committee.

Murren received a B.A. in chemistry and history from Duke University, and an M.D. in 1984 from the Loyola-Stritch School of Medicine. He completed internship and residency in internal medicine at St. Vincent's Hospital in New York. In 1988, he accepted a postdoctoral fellowship in medical oncology at Yale-New Haven Hospital, where he was an attending physician as well as an associate professor of medicine.

Murren was one of the founders of the Nevada Cancer Institute, established in 2002. He was a member of the institute's Board of Directors and served as an adjunct faculty member.

Murren is survived by his wife Nancy; son John; mother Jean Perkins Murren; brothers Jim and Michael; sister Kathie; sisters-in-law Heather Hay Murren and Mary Kay Murren; brother-in-law George Koether; and several nieces and nephews. His father, Connecticut State Representative John Henry Murren, died in 1990 from melanoma at age 59.

Joseph E. Walther, Institute Founder

Joseph E. Walther, who used the proceeds from the sale of his hospital to found the Walther Cancer Institute at Indiana University Medical Center, died Dec. 10. He was 93.

The institute supports research at several universities and is credited with funding important work in the treatment of testicular cancer and using umbilical cord blood in the treatment of cancers that require bone marrow transplants. Walther retired as president and chief executive officer of the institute in 2002.

"He was a remarkable man who had a major impact on cancer research in Indiana," said John Durant, former executive vice president of the American Society of Clinical Oncology who served as a consultant to Walther and the institute. "He did a tremendous amount of good with the proceeds of the sale of his hospital."

An Indianapolis native, Walther earned his medical degree from Indiana University School of Medicine in 1936. Prior to World War II, he served as a physician for Pan-American Airways on Midway Island. During the war, he served as a surgeon in the U.S. Army Air Force in the Pacific. He won the Silver Star, Soldier's Medal, Bronze Star, and Air Medal, and logged over 30 combat missions. He remained active in the Air Force Reserves for 24 years, retiring as a colonel.

Walther's philanthropy began in 1956 when the Winona Memorial Foundation, named in memory of his mother, was chartered as a charitable organization. He founded Winona Memorial Clinic as his private practice in 1947 and built Winona Memorial Hospital, a 278-bed facility that opened in 1966. After his wife, Mary Margaret, died of colon cancer in 1983, Walther sold the hospital and, in 1985, began Walther Cancer Institute with the $30 million in proceeds.

Survivors include five children, Mary Ann Margolis, Joanne Landman, Diane Paczesny, Kurt Walther, and Karl Walther; eight grandchildren; and six great-grandchildren.

William O. Baker, Bell Labs President

William Oliver Baker, a former president of Bell Labs who served on the National Cancer Advisory Board from 1974 to 1980, died Oct. 31 at a nursing home in Chatham, N.J., of respiratory failure. He was 90.

Baker led Bell Labs from 1973 to 1979. He also served as a science advisor to U.S. presidents.

He is survived by a son, Joseph Baker, of Morristown, N.J. His wife Frances Burrill Baker, died in 1999.

Funding Opportunities:

Pancreatic Cancer Research RFA

Letter of Intent Deadline: Feb. 10. Application Deadline: Feb. 27. Grants can be submitted in one of two areas: 1. screening for the early detection of pancreatic cancer and 2. novel therapies in pancreatic cancer. The initiative encourages, but does not require, the development of integrative and collaborative teams of investigators from within a single institution or among several institutions. Proposals that exhibit leveraging of institutional resources and the attainment of major new programs, such as a SPORE or P01, are encouraged.

Grants, which will begin funding in June, will be awarded for a period of up to three years with a maximum funding of $250,000 a year, which includes a maximum 10 percent for indirect costs.

Letters may be e-mailed to Jeanette Campo at: Jcampo@cablevision.com. Inquiries and applications: The Lustgarten Foundation 516-803-2304; www.lustgarten.org.

Program Announcements

PAR-06-104: Improving Diet and Physical Activity Assessment. NCI and participating organizations invite research applications that advance the quality of measurements of dietary intake and physical activity pertinent to cancer and/or other pathologies through support of research on improved instruments, technologies, and/or statistical/analytical techniques. The PAR is available at http://grants.nih.gov/grants/guide/pa-files/PAR-06-104.html.

Inquiries: For NCI--Amy Subar, or Richard Troiano, 301-594-0831 or 301-435-6822; subara@mail.nih.gov or troianor@mail.nih.gov.

PAR-06-088: Innovations in Biomedical Computational Science and Technology Initiative. Application Submission Date: Feb. 26. NIH seeks SBIR grant applications in biomedical computing or biomedical information science and technology. The PAR is available at http://grants.nih.gov/grants/guide/pa-files/PAR-06-088.html.

Inquiries: Jennifer Couch, 301-435-5226; couchj@mail.nih.gov

PAR-06-089:Innovations in Biomedical Computational Science and Technology Initiative. The funding opportunity solicits Small Business Technology Transfer grant applications from small business concerns. The PAR is available at http://grants.nih.gov/grants/guide/pa-files/PAR-06-089.html.

PA-06-101: Research on Clinical Decision Making in Life-Threatening Illness. National Institute of Nursing Research and NCI invite applications for research that would include life-threatening illnesses that may be cured in early stages such as breast cancer. The PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-06-101.html.

Inquiries: For NCI--Wendy Nelson, 301-435-4590; nelsonw@mail.nih.gov.

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