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BMS Execs Knew Of Flaws In ImClone Plan For C225 Prior To $2-Billion Licensing Deal

Bristol-Myers Squibb executives were aware of many of the fundamental flaws of ImClone's program for development of C225, but chose to proceed with the $2-billion licensing and investment deal, company documents show.

The Bristol and ImClone memoranda were obtained by Congressional investigators and made public at a dramatic and meticulously researched six-hour hearing last week.

Along with theatrics of a fleeting appearance by ImClone's former president and CEO Samuel Waksal, the June 13 hearing of the

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In Brief:

NCAB Grants Three MERIT Awards; Rimer To Leave NCI For Post At UNC

THREE NCI-FUNDED R01 principal investigators were granted MERIT award status for their competing continuation grants by action of the National Cancer Advisory Board at its meeting last February and announced last week. They are: **Mary Hendrix**, University of Iowa; **Terumi Kohwi-Shigematsu**, University of California, Lawrence Berkeley Laboratory; and **Satya Prakash**, University of Texas Medical Branch, Galveston. The investigators met the rigorous criteria NCI applies for the NIH Method to Extend Research in Time award (R37): Their competing renewal (type 2) R01 grant applications were judged by peer review to be in the top 5th percentile of applications; the PIs were recognized as established leaders in their fields, as attested to by their publication records; and NCI and the NCAB determined that the research studies proposed are of special importance and have substantial long-term relevance to the NCI mission. The awardees will be fully funded for the periods specified in their applications and they will have the opportunity to receive an additional round of competitive funding without submitting a full, new application for peer review. NCI MERIT award policy is described at *http://grants2.nih.gov/grants/guide/notice-files/not96-033.html*. . . . **BARBARA RIMER**, founding director of the NCI Division of Cancer Control and Population Sciences, said she plans to leave NCI later this year to take a position at the University of North Carolina at Chapel Hill. Rimer made the announcement in an email to the division staff earlier this week. She informed NCI Director **Andrew von Eschenbach** that she has accepted a position as professor of health

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More Revelations: C225 Study Used A Less Rigorous Protocol

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Subcommittee on Oversight and Investigations of the House Committee of Energy and Commerce produced a complex picture of institutional dysfunctions, disconnects, and denials that have now elevated the ImClone scandal to the level of notoriety equal to that of Enron.

The hearing has added a new dimension to analysis of what went wrong:

—FDA gave C225 the Fast Track designation based on a version of the protocol that had a more rigorous definition of enrollment criteria than the protocol that was actually used to accrue the majority of patients. The agency was unaware that the original version of the protocol had been replaced by a version that had lax requirements that experts in colorectal cancer would consider unacceptable.

—Bristol officials knew that ImClone's rationale for selecting the C225 dose for metastatic colorectal cancer was questionable, and that toxicity was not well characterized. These flaws were later noted by FDA as reasons for rejecting the filing (**The Cancer Letter**, Jan. 4, Jan. 11).

—During due diligence review, Bristol had audited the data for colorectal cancer patients who responded to the experimental combination therapy of C225 and CPT-11, discovering that the response rate was lower than the company claimed. Consultants who audited the ImClone data for Bristol also detected that at least some of the patients classified as responders were ineligible for enrollment.

It is unclear whether Bristol officials realized that response rate to C225 and CPT-11 in the pivotal trial was below the level that FDA officials said they would consider meaningful.

—At the time Bristol completed the transaction, the company didn't have the results of ImClone's trial of C225 as a single agent. The trial, which was ongoing, was a crucial element of ImClone's highly unusual approval strategy.

—An internal e-mail from Peter Ringrose, president of Bristol's Pharmaceutical Research Institute, indicates that on Oct. 12, 2001, Samuel Waksal said FDA was "pleased" with the outcome of the single-agent trial and confirmed that the C225 application would be presented to the FDA Oncologic Drugs Advisory Committee Feb. 28, 2002. "He reckons they will be on the market in March," Ringrose wrote.

Committee staff disputes these apparent claims by Waksal.

"According to committee staff interviews with FDA personnel, no one at FDA spoke to ImClone about the single-agent data on or around Oct. 12, 2001, and FDA had never placed [C225] on the agenda for the February 2002 ODAC meeting," the committee staff report said. "The submission of the single-agent study to FDA was not completed until Dec. 4, 2001."

Bristol officials also knew of problems with obtaining patent protection and scaling up manufacturing of C225, a monoclonal antibody. Future development was not straightforward, either. Since clinical trials were conducted with a variety of doses of C225, it was unclear which doses should be selected for future trials.

Competition, particularly from Iressa, an AstraZeneca compound, appeared to be a problem, too, Bristol officials knew.

"On the whole, this remains a very high risk opportunity," Laurie Smaldone, BMS senior vice president of Worldwide Regulatory Science, wrote in a June 14, 2001, email listing potential pitfalls. "The list incorporates concerns that Beth [Seidenberg] and I have reviewed together, some can be structured into an arrangement to move forward in increments, but others have landed very recently in due diligence process that are more concerning and weigh

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negatively."

The email was addressed to Ringrose.

A Bristol audit of a subset of patients enrolled in the pivotal trial of C225 and CPT-11 showed that four patients classified as by ImClone as partial responders didn't have progressive disease at the time they were enrolled in the trial.

"If these four cases were thrown out, then the highest possible [response rate would be] 12.5%," the radiologist wrote in an e-mail dated Aug. 30, 2001. "However, we have not conducted a strict review of all the cases, and it is likely that if we carefully reviewed all of the cases, we would throw many of them out on the same basis."

Bristol conducted a complete audit of the ImClone application only after it was jettisoned by FDA.

According to an analysis by Raymond Weiss, an oncologist and trial auditor hired by the committee, of the 139 stable and progressive disease patients on the trial, 37, or 26.6%, were ineligible. Of these patients, 25 had blood counts or serum chemistry values that didn't meet protocol requirements, and 15 of them were given exemptions to be enrolled. Such exemptions are almost never granted either in cooperative group trials or in pharmaceutical company trials.

The ImClone Biologics License Application focused on the 121 patients who had progressive disease. However, one of these patients was lost without any explanation, Weiss said.

The ineligibility of 26.6 % is extraordinary, Weiss said to **The Cancer Letter**. By way of comparison, a recent broad sample of 520 patients treated in Cancer and Leukemia Group B studies showed that only 3 percent of patients were ineligible.

"Generally, these 3 percent are due to human error," said Weiss, chairman of the CALGB Data Audit Committee.

Similarly, enrollment exemptions at CALGB require the approval of group chairman, and are extremely rare. "It would be an extraordinary circumstance when a waiver is given," Weiss said. "I can recall seeing two in audits in the past 10 years."

Former ImClone president and CEO Samuel Waksal declined to answer questions from the committee, claiming his rights under the Fifth Amendment to the U.S. Constitution. A day earlier, on June 12, Samuel Waksal was arrested and charged by the U.S. Department of Justice and the Securities and Exchange Commission. He was freed after posting $10 million bail.

In prepared remarks, Harlan Waksal, who succeeded his brother as ImClone president and CEO, noted that Bristol's investment was "a huge vote of confidence" in C225, as was the involvement Memorial Sloan-Kettering Cancer Center oncologist Leonard Saltz in the company's trials.

"Despite these encouraging signs, the FDA refused to file ImClone's application for Erbitux," Waksal said. "With the benefit of 20/20 hindsight, we now know that we could and should have done a better job in putting together our application package."

Harlan Waksal acknowledged not having heard Weiss's testimony, which preceded his, and seemed unfamiliar with the questions raised by Weiss.

Waksal said FDA was aware of the company's decision to change the enrollment criteria for its pivotal clinical trial. "The protocol modifications were minor," Waksal said. "There were protocol deviations that took place, where doctors have gone ahead and made changes in the doses of irinotecan, primarily to increase the dose of irinotecan that was used in those patients."

A webcast of the hearing available at: *http://energycommerce.house.gov/107/hearings/06132002Hearing587/hearing.htm*. Also available is the investigation report by the committee staff, copies of submitted testimony, and the complete text of the Weiss report.

The committee investigation continues.

SEC Puts ImClone On Notice That It May Bring Action

ImClone Systems Inc. June 19 received a "Wells Notice" from the staff of the Securities and Exchange Commission, indicating that the staff is considering recommending the Commission bring an action against the company.

The SEC letter stemmed from "the company's disclosure immediately following its receipt of a 'refusal to file' letter from FDA on Dec. 28, 2001," the company said.

Initially, ImClone press releases maintained that FDA's action stemmed from the absence of "train of documentation" in the company's trial of C225 and CPT-11 for third-line treatment of advanced colorectal cancer, and as soon as documentation is provided, the application would be back on track.

The RTF letter, which was obtained by **The Cancer Letter**, described fundamental flaws in

protocol design and the conduct of studies (**The Cancer Letter**, Jan. 4, Jan.11). According to materials that emerged in the Congressional investigation, officials at Bristol-Myers Squibb were made uncomfortable by statements made by Samuel Waksal immediately after the application was refused.

"At this point, it's clear we'll need to go beyond our original comment, and decide what we want to say about the issues raised by the FDA in this letter," Nancy Goldfarb, who at the time was the BMS spokesman, wrote in an e-mail Dec. 30, 2001, two days after the RTF letter was received.

Under the Wells process, the company will be given the opportunity to respond in writing to the Wells Notice before the staff formally recommends prosecution.

ImClone officials said the company would "respond promptly and thoroughly" to the SEC notice.

Last month, Samuel Waksal received a Wells Notice, which caused him to resign.

Expert Raymond Weiss Finds "Incredible" Protocol Violations

Congressional investigators hired Raymond Weiss, an oncologist and clinical trials auditor, to evaluate the ImClone development program, based on materials obtained from ImClone, Bristol-Myers Squibb, and FDA. The excerpted text of the document follows:

The 9923 Protocol

This study was an open-label, phase II study designed to "determine the response rate of cetuximab [C225] administered in combination with irinotecan [CPT-11] to patients with advanced colorectal cancer who are refractory, i.e., have demonstrated stable or progressive disease to treatment with an irinotecan-containing regimen" and "to determine the time to progression, evaluate the safety/toxicity profile of cetuximab in combination with irinotecan [and] assess the Quality of Life" in patients treated with this two-drug combination.

"Refractory" to prior therapy means that an adequate attempt to cause tumor regression with a particular therapy has been made, and the cancer progressed despite the treatment.

Version 1.0 of the protocol was dated Aug. 2, 1999. Version 2.0 was dated Oct. 18, 1999. It was not originally designed to be a study used as the basis for submission of a [Biologics License Application] for marketing approval. After accrual of most of the patients entered and discussions with the FDA by ImClone officials in 2000, the purpose of the clinical trial was modified so it would serve as a registration study.

A meeting was held between ImClone and FDA officials in August 2000, at which time the understanding was that [study] 9923 would be the registration study with a plan for accelerated approval designation.

The eligibility criteria in Version 1.0 stated the patient must have demonstrated "progression of disease [metastases] after completing a minimum of two courses of a regimen containing irinotecan." The definition of a "course" of irinotecan was not stated.

These eligibility criteria were changed in Version 2.0 of the protocol. In the newer version, the patient had to have "documented stable disease (must have received a minimum of 12 weeks of irinotecan therapy) or progressive disease at any time after receiving an irinotecan-containing regimen." The irinotecan dose and administration frequency were to be the same as was being used for the patient when progressive disease occurred prior to entry on the trial.

Documents regarding the August 2000 FDA meeting indicate FDA officials had concerns about the study design, and whether there was sufficient documentation a patient had clearly failed irinotecan therapy before study entry. The whole scientific basis for clinical use of this new drug was that the combination of irinotecan and cetuximab represented a potentially effective, third-line therapy for patients with metastatic CRC after failing prior 5-FU and irinotecan therapy.

The ImClone officials stated their belief that "there exists a core of patients who had clearly refractory disease for whom the evidence of antitumor activity is compelling" in the results of the study conducted to that time point. In order to prove that both drugs had to be administered together to obtain an antitumor effect (while accepting the potential for toxicity of both drugs), the patient's cancer had to demonstrate clear resistance to any further therapy with irinotecan.

The eligibility criteria as understood by FDA officials (according to minutes of the meeting in August 2000), were that patients would have to have either stable disease defined as <25% volume change in the measurable cancer lesions or progressive disease defined as a >25% change "after two courses of irinotecan." This latter point is what the protocol

Version 1.0 stated.

There is a difference in the definition of what constitutes an eligible patient between Version 2.0 of the protocol and the understanding of the FDA officials at this meeting. Version 2.0 (dated 18 October 1999) loosened the eligibility requirements to "progressive disease at any time after receiving an irinotecan-containing regimen."

No minimum amount or duration of therapy with irinotecan was required in Version 2.0. The final conclusion of the FDA officials was that the study design was "probably acceptable."

Study 9923 Conduct

There were 139 patients entered on 9923, 121 with progressive cancer after irinotecan and 18 with stable disease. Somewhere one patient was deleted, because all reports subsequent to 2000 indicate there were 120 patients with progressive disease who were treated on this study.

In January 2002, BMS staff reviewed and critiqued the BLA. According to this review, an incredible 37 patients (26.6% of the 139 patients entered) "had at least one inclusion/exclusion" criterion "that did not qualify them to be eligible for the study," and eight of them "had more than one reason for ineligibility."

Twenty-five of these 37 patients had initial blood counts or serum chemistry values that were outside the range required by the protocol. Another incredible point is the fact that 15 of these 25 patients "were given exemptions to be enrolled in the study." The purpose of eligibility criteria is to define what patients have organ function and disease parameters that make them a suitable candidate for the clinical trial. Once these criteria are set, exemptions are not given. If this is done, it could invalidate the results of the study. Rates of ineligibility should not be more than single digit percentages in any clinical trial.

Another set of major deviations in the study was changing the dose and administration frequency of the irinotecan. This drug was supposed to be administered in the same pattern as had been done before the patient went on the 9923 study. Irinotecan is most often administered in a schedule of four consecutive weekly doses, with a 14- to 21-day break before another series of four consecutive weekly doses is begun. However, it may also be given in a schedule of once every three weeks. Thus, there were variations in the manner patients might receive the irinotecan on the study. There are directions in the 9923 protocol regarding delaying one or more of the weekly cetuximab infusions for any significant toxicity that might occur, but there were no directions for modifying the irinotecan dose or frequency. It is standard practice in cancer treatment protocols to provide specific directions for changes in the drug doses and/or treatment frequency based on the degrees and kinds of therapy toxicity encountered. In my opinion, this point is a design flaw in the 9923 protocol that could lead to problems in interpreting the results.

Although the protocol specified that the irinotecan was to be given in the same dose and schedule as previously when disease progression occurred, with no dose increases, at least 17 patients had major changes in the irinotecan dose when entered on the study, including dose increases. This fact adds further uncertainty regarding the validity of any results from this study.

Flaws in the design of the 9923 protocol were also expressed publicly by three prominent medical oncologists after the publication of the RTF (**The Cancer Letter**, Feb. 15). For example, one oncologist stated: "Overall, this is a protocol that asks the wrong questions, and then is not tightly written and efficient. The protocol generates far more questions than it could ever answer. It is a blueprint for the production of vague answers." Another oncologist stated that "the entry criteria on the study were so vague it can't be determined whether all the patients in the trial are indeed refractory to prior therapy."

Results of 9923 Study

An independent panel of two medical oncologists and two radiologists was convened by ImClone to review the case records and the radiographs (the Independent Response Assessment Committee or IRAC) and evaluate the responses, or lack thereof, of all patients entered whether counted as "progressive disease" or "stable disease" on the irinotecan therapy given prior to study entry.

Many of these same radiographs were then reviewed by consultants to BMS. A comparison of these two sets of evaluations indicates the subjectivity that can occur in making assessments of the same CT scans. For example, eight patient cases the IRAC had categorized as achieving a Partial Response, which is defined as at least 50% regression of the measurable tumor lesions visible on serial radiographic studies (almost always CT scans), were categorized by the BMS consultants as achieving only stable disease.

A total of 23 patients were categorized as

achieving a PR by the investigators, while 27 were so categorized by the IRAC. Twenty of these patients were considered to have a PR by both the investigators caring for the patients and the IRAC for an overall response rate of 16.5%.

Of the 121 patients coded as having disease progression prior to entry, the IRAC and BMS agreed that a PR had been achieved in only 16 cases. Now the response rate was only 13.2% where both sets of consultants agreed. In addition, three patients whose response after treatment with irinotecan and cetuximab was called SD by the IRAC had it changed to "progressive disease" by the BMS review.

The number of responders where both BMS and the IRAC would agree with the interpretation of the scans is now possibly below the point of real meaning. Most clinical oncologists would agree that at least 15% of patients treated with an agent should achieve a PR to be meaningful.

In fact, the ImClone officials themselves discussed with the FDA officials in the August 2000 meeting that at least a 15% response rate must be achieved to be "clinically meaningful." A response rate lower than 15% would only be important if a randomized study with half the patients receiving a new treatment and half receiving only supportive care indicated a significantly longer survival for the treated group. Such is indeed the case with irinotecan, as has been established scientifically. Although the response rate of irinotecan in patients who had failed 5-FU therapy was only approximately 13%, overall survival was significantly improved by irinotecan therapy when compared in a randomized study to supportive care only (without systemic anticancer therapy). Of course, such could also be the case with cetuximab if it were subjected to the same sort of randomized study as has been accomplished with irinotecan.

In the context of the disparities regarding which patients achieved a response and to what degree, it is worth quoting the statements made by Dr. Sam Waksal at a conference call to the financial community on Dec. 31, 2001. He said the IRAC came to a similar conclusion about responders as did the investigators. He further stated that all CT scan films had been reviewed "internally by us, they have been reviewed by the sites themselves where the conclusions were made and by the IRAC, and again there is *concordance across the board*" (italics are mine).

Overall, there were 38 patients where the category of disease status prior to study entry was in disagreement between the IRAC and the investigators. In addition, of the 35 patients whose radiographs were reviewed by BMS consultants, there was disagreement between the IRAC and BMS consultants in the response category for 14 cases, which is more than a third of the sample.

The results of this study were published in an abstract submitted for the annual meeting of the American Society of Clinical Oncology. The abstract submission deadline is early in the month of December prior to the meeting (in this case it would have been December 2000). The abstract stated that the patients were refractory to both irinotecan and 5-FU, and 121 patients were said to have been entered. Whenever any study data are presented at this meeting, only 10 minutes are allowed for the oral presentation. Thus, only a limited amount of information can be presented.

It was stated patients were entered who had "documented progression of metastatic disease on irinotecan" and "no intercurrent chemotherapy could have been given between irinotecan failure and protocol entry." The abstract states 121 patients were entered, but the oral presentation involved only 120 patients. A total of 27 of these 120 patients (22.5%) were said to have achieved a PR, which is the number determined by the IRAC.

Case Reviews

I reviewed with the WRAMC radiologist the film sets of the three cases where selected CT scan pictures of metastatic lesions were shown at the ASCO presentation.

These were Cases #615, #644, and #683. It is noteworthy that Case #644 was coded as having achieved only a SD status by the IRAC after treatment on the study. Although this patient indeed had regression of some metastatic lesions in the lungs, a pelvic mass was at the same time invading and encroaching more on the urinary bladder in the pelvis.

It is also noteworthy that Case #615 had irinotecan therapy only from 15 November 1999 to 6 December 1999, and assuming the drug was given weekly, only four doses could have been given. A chest X-ray done on Jan. 4, 2000, a month after the last irinotecan dose, did indeed show a new nodular density in the right mid lung, indicating cancer progression. Although this patient did meet the revised eligibility criteria of the study in Version 2.0 of the protocol, he would not have been eligible based on the understanding of the FDA of the eligibility criteria where the patient would have had to be treated with

"two courses" of irinotecan.

If the drug is given weekly in four consecutive weeks, then this would constitute a "course." A second "course" of four weekly doses would then be given after a rest interval without treatment of 14 to 21 days. This patient did not receive two courses of irinotecan therapy prior to entry on the 9923 study.

An example of clear ineligibility for this study is Case #643. This patient received his last dose of irinotecan on March 31, 1999. He was then treated with oxaliplatin (another investigational agent for CRC) between June 1999 and August 1999. It must be recalled that according to the protocol no other chemotherapy should have been administered between the time the patient was last treated with irinotecan and the time of study entry, a point that was reiterated in the ASCO abstract presentation. Nonetheless, he was entered on the study on March 14, 2000.

Another example of problems with this study is Case #704. The ASCO abstract states the patients were refractory to both irinotecan and 5-FU. The case report form for this particular patient indicates that the only chemotherapy the patient had received prior to study entry was irinotecan. There is no evidence the patient ever received 5-FU.

The serial radiographs of Patient #683 were reviewed. This patient had clear progression of his cancer on irinotecan, so he met the eligibility criteria of 9923 in this regard. In response to the 9923 therapy he had definite shrinkage of the cancer lesions in the liver, which regressed at least 50%, but the response lasted only three months before disease progression occurred once more. This is a rather short interval, but one must recall the patients treated on this study had undergone much prior systemic therapy and sometimes radiation therapy also. Such a short interval of response would be expected from a drug with some modest antitumor efficacy, but not one that had been espoused as another blockbuster anticancer agent.

Single-agent Study (#0141)

In order to assess the effect of cetuximab as a single agent, this study was initiated in early 2001.

A total of 57 patients were entered on this study, the results of which were presented at the May 2002 meeting of ASCO. The patients entered had to have "documented progressive disease at any time after receiving an irinotecan-containing regimen." The title of the abstract presented states the patients were refractory to irinotecan, and six patients were stated to have achieved a PR.

The BMS review of the BLA in January 2002 indicates that there was uncertainty regarding the fact that all patients were truly refractory to irinotecan (meaning they had "documented progressive disease") before being entered on the study. The BMS reviewers stated that "irinotecan refractoriness can be inferred" for 11 of the 57 patients, but "the data collected in this trial are insufficient to determine irinotecan refractoriness for any patient." Two of these 11 patients were verified to have had a PR by the BMS review.

Although six patients were stated to have responded to cetuximab given by itself in this study, the BMS review indicates that one of these patients may not truly have had a response. The final opinion of the BMS staff was "there are five patients....whose data compellingly support a determination of partial response to the single agent" cetuximab. Although it is apparent this agent does have some antitumor activity by itself, the rate of such responses, with a solid assessment of the response, is only five (8.7%) of the 57 patients.

Summary

It appears that cetuximab has some antitumor effect for metastatic CRC when used as sole therapy as reported in an ASCO presentation in May this year. Cetuximab also appears to have some effect when given in conjunction with irinotecan despite disease progression having occurred when the patient was treated previously with irinotecan, as was reported at the May 2001 ASCO meeting.

However, for some patients it is unclear whether or not the irinotecan makes any contribution to the therapy. The irinotecan perhaps only adds toxicity to the therapy and no benefit.

The 9923 study has major problems in adherence to the eligibility criteria and the irinotecan dosing. In addition, the assessments of response are subject to considerable variation depending on who reviews the CT scans. After examining a great deal of the information assembled by the House Committee staff, I agree with the assessment of the three oncologists as published.

Based on the results of the 9923 study available for my review, I am unable to determine if this drug has meaningful activity in CRC and adds to patient survival after failure of all available standard therapy. The single-agent study does show the drug has an effect for a rare patient, but a reliable response rate is <10%, a level that possibly provides little patient benefit or improved survival.

In Brief:

Rimer In Note To Staff: Hiring Has Become "Difficult" At NIH

(Continued from page 1)

behavior and health education at the UNC School of Public Health, and deputy director for population sciences at the Lineberger Comprehensive Cancer Center. She also said she will develop a university-wide Health Communications Program. She plans to leave NCI in mid-November. Rimer came to NCI from Duke University in 1997 to form the DCCPS, which is responsible for research programs in populations, behavior, surveillance, special populations, outcomes, and other aspects of cancer control. Prior to her appointment, she served as chairman of the National Cancer Advisory Board, leading the board during its controversial 1997 deliberations on guidelines for mammography screening. Rimer received her B.A. and M.P.H. from the University of Michigan and her doctoral degree from the Johns Hopkins School of Hygiene and Public Health. She spent 10 years at Fox Chase Cancer Center, where she served as director of behavioral research. In 1991, she became director of the Cancer Prevention, Detection and Control Research Program and professor of community and family medicine at Duke. In her email, Rimer praised the DCCPS staff profusely, but noted that, "It has become more difficult to hire and reward people, a change from the early days of my role here. I hope that Dr. **[Elias] Zerhouni** [NIH director] and Dr. von Eschenbach will return NIH to the less bureaucratic period in which science truly flowered." . . . **THE "KIRSCHSTEIN AWARDS"** is the new name of the National Research Service Awards, the NIH training grants program. The new name honors NIH Deputy Director **Ruth Kirschstein**, a 46-year veteran of NIH who served as acting director from January 2000 until last month. **Sen. Tom Harkin** (D-IA) announced the new name, an expression of thanks to Kirschstein from members of Congress. Kirschstein also was honored recently by the Federation of American Societies for Experimental Biology, which named the garden at FASEB headquarters in Rockville, Md., after her. . . . **DONALD FREDRICKSON**, NIH director from 1975-1981, died June 10 of a heart attack. He was 77. After leaving NIH, he served as president of the Howard Hughes Medical Institute from 1984-1987.

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