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Under Ultimatum, NIH Databases Remove "Misconduct" Tags From Papers By Fisher

Users of medical literature databases run by NCI and the National Library of Medicine have been finding an announcement tagged to papers that list Bernard Fisher as an author:

[SCIENTIFIC MISCONDUCT--DATA TO BE REANALYZED]

Another tag proclaimed:

[SCIENTIFIC MISCONDUCT--REANALYSIS OF NSABP PROTOCOL B-06 AVAILABLE VIA PDQ, CANCERNET, OR CANCERFAX]

Scientific misconduct? By whom?

(Continued to page 2)

In Brief

Judge Declines To Block NCI Contract Award

A US Court of Federal Claims judge denied a motion for a temporary restraining order that would have prevented NCI from awarding a contract for operations of the Frederick Cancer Research and Development Center.

The order was sought by DynCorp Advanced Technology Services Inc., parent company of Program Resources Inc., which has held the Frederick contract for the past seven years.

DynCorp's suit, filed Feb. 15 in the US Court of Federal Claims, seeks to prevent NCI from awarding the contract. Following a closed hearing Feb. 16, Judge Thomas Hodges Jr. ruled that "a contracting officer has wide discretion in the application of procurement regulations.

"To prevail, plaintiff must show by clear and convincing evidence that the agency's determination was unreasonable or irrational," he wrote.

PRI offered "only the most general and conclusory arguments in support of its contention that the change in the contract period was 'so substantial' that a new solicitation was required," Hodges wrote.

PRI's contract for the Frederick center expires March 25.

Jury Awards $14 Million To Medenica Patient

A jury in Hampton County, SC, awarded $14 million in damages to a couple who claimed medical malpractice by Hilton Head Island physician Rajko Medenica.

The jury found that Medenica was negligent in his treatment of Gayle Taylor, a breast cancer patient. (**The Cancer Letter**, April 30, 1993). As a result of treatment with the drug mitomycin-C, Taylor developed hemolytic uremic syndrome, the plaintiff claimed.

The award included $10 million in punitive damages.

Medline, Cancerlit Remove "Misconduct" Tag From Papers

(Continued from page 1)

The HHS Office of Research Integrity has not announced the findings of its investigation of Fisher. The only misconduct related to his case was committed by Roger Poisson, a Montreal surgeon.

Does the Poisson case warrant inserting the "misconduct" tag on at least 88 papers that list Fisher as an author?

Among those papers are primary studies that clearly include Poisson's fraudulent data. However, also tagged were publications in which Fisher expresses his opinions, a review of literature by **The Cancer Letter** confirmed. The review also found that publications are flagged inconsistently in Medline and Cancerlit, two databases operated by NIH. Also, at least one paper was flagged by Cancerlit even though the data was obtained prior to the first documented incident of fraud at Poisson's hospital.

Last week, an attorney for Fisher gave NIH an ultimatum: Remove the tags within 48 hours or face legal action. In response, officials at the HHS Office of Research Integrity ordered that the words "scientific misconduct" be struck from the tags.

The question that remains is what is to be done with the remainder of the tag: DATA TO BE REANALYZED. Should it continue to adorn Fisher's "The Evolution of Paradigms for the Management of Breast Cancer: A Personal Perspective"?

"It's very simple," said Robert Charrow, Fisher's attorney. "They ought to pull the flags off all the papers until they can figure out what to do.

"They likely owe Dr. Fisher some damages," Charrow, of the Washington firm Crowell & Moring, said to **The Cancer Letter**.

Charrow contends that NIH officials went beyond warning cancer researchers about fraudulent data from Montreal.

"It appears that NLM and NCI designated articles without regard to the data in those articles, and instead, based their decision solely or largely on whether Dr. Fisher was an author," Charrow wrote in his Feb. 15 letter to NIH Legal Advisor Robert Lanman.

In an interview with **The Cancer Letter**, Lyle Bivens, ORI director, said the wording of the tag was an oversight on his part.

Bivens said the tags were written by the National Library of Medicine. ORI provided the library with a list of papers that were believed to include data from Poisson's institution, St. Luc Hospital, he said.

"We didn't ask for a 'scientific misconduct' flag on it," Bivens said "NLM is used to that when they get a request from my office, because usually it is as a result of a misconduct finding.

"I was not explicit enough in what the statement should have been," he said.

Bivens said that earlier this week he directed that the words "scientific misconduct" be removed. "Today I sent a memo to NLM asking that they take 'scientific misconduct' label off," he said in an interview Feb. 21.

An NLM official contradicted Bivens's statement, saying that the tag was written by ORI.

In an interview with **The Cancer Letter**, Lois Ann Colaianni, NLM associate director for library operations, said ORI had specifically asked the library to use the words "scientific misconduct."

Colaianni said NLM did not select the papers for tagging.

"We had nothing to do with identifying the papers," she said. "It was through a special request that we labelled these.

"Generally we steer away from labeling papers. We have retractions, and errata, and comments. At the time these went in as comments. However, there was concern that it wasn't enough to cause people to read the reanalyzed data," she said.

From documents and interviews **The Cancer Letter** has learned that the ORI staff selected the papers that were ultimately tagged.

Removing the words "scientific misconduct" does not wipe out the damage to Fisher and to scientific literature, Charrow said.

"Had this language been contained in a news

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report and had Medline and Cancerlit been a private publication, their actions would have constituted defamation," Charrow said.

"While the government may believe it is immune from defamation claims, private publishers are not," Charrow said. "We are advising the scientific community that we will take action against anyone who republishes the defamatory statements contained in Medline."

The NIH tags are beginning to filter into medical literature. Two flags can be found on p. 318 of the Feb. 15 issue of the Journal of the National Cancer Institute.

Fisher Case Different From the Start

ORI's actions in the Fisher case were unprecedented, Bivens said.

"This is the first case we've had where we put out a notification prior to any scientific misconduct finding," he said in an interview.

"We made a commitment to let the clinical community know even prior to an investigation if there is a problem with publications that may inform treatment decisions," he said.

Asked why ORI decided to go beyond flagging publications that involved Poisson data, Bivens said, "As the situation developed, it became a possibility that either bad data or suspect data might be contained in other publications.

"That is the primary question we are asking."

A review of publications was an essential part of the Fisher case, Bivens said. ORI had to compile its own list because Fisher's cooperative group, the National Surgical Adjuvant Breast & Bowel Project, failed to provide a complete list of publications to the investigators, he said.

"We never have gotten a complete list of publications from NSABP that we feel we need," Bivens said. "We needed to find out what publications had been submitted from NSABP when it was known that St. Luc data was shown to be falsified."

The Anatomy of a Tagging

From documents and interviews, **The Cancer Letter** was able to reconstruct the process that resulted in the flagging of Fisher's publications.

On April 25, 1994, NCI Director Samuel Broder wrote a memorandum to Donald Lindberg, NLM director, in which he asked the library to help the Institute ensure that the databases denote serious error, fraud or scientific misconduct in research supported by NCI.

The memorandum, which did not mention Poisson, Fisher or NSABP, sought to set up a mechanism for NCI and NLM to work together.

In a May 4 memo, Lindberg informed Broder that Colaianni was designated to work with NCI on denoting in the literature episodes of misconduct and fraud.

Broder designated Susan Hubbard, head of the NCI International Cancer Information Center, to work on the project. ICIC runs the Cancerlit database.

Initially, ORI officials requested that NCI compile a list of papers that could have been affected by fraud.

However, documents indicate that NCI officials did not perform the selection of papers that were subject to flagging. Instead, NCI provided to ORI a list of NSABP publications, leaving it to the investigators to decide which publications ought to be flagged.

A memorandum from Bivens dated May 20 and addressed to Colaianni confirms that ORI investigators were working with a list of NSABP publications, crossing out the publications that in their judgment were unrelated to the clinical trials in question.

Attached to the memorandum was a list on which some entries were marked with an "X." The library was instructed to avoid flagging the articles so marked.

However, in the memorandum, Bivens said the list was compiled with the help of NCI. In an interview with **The Cancer Letter**, he repeated that statement.

"NCI gave us a list," Bivens said. "NCI identified the articles as containing data that might need to be reanalyzed."

Sources said that the same scientific papers were to be flagged in both NLM's Medline and NCI's Cancerlit.

However, Charrow's letter includes 88 "unique identifier" numbers for publications authored by Fisher and contained in Cancerlit and 19 identifier numbers for publications cited in Medline. A review of the databases by **The Cancer Letter** indicates that many of the articles flagged in Cancerlit were not flagged in Medline.

"The action that was taken was to try to flag articles that had data from St. Luc," Hubbard said to **The Cancer Letter**. "The purpose was not to make the cancer community feel that Dr. Fisher was responsible for scientific misconduct. The language

used did not make that clear.

"If we were to do it again, we would all do it differently."

Hubbard said that once NSABP's reanalysis of the B-06 study is published, the "data to be reanalyzed" flag will be removed from both Medline and Cancerlit. Instead, a comment will refer readers to the publication of the reanalysis.

Can All Data From St. Luc Be Excluded?

The controversy over what is to be flagged is likely to rekindle the question of whether the government has the legal authority to exclude all St. Luc data from the trials, regardless of whether the data were submitted by Poisson or other researchers.

So far, the government has been guided by the ORI recommendations contained in the 1993 report on the investigation of Poisson. "The reliability of the entire data set from St. Luc Hospital remains questionable," Bivens wrote in a memorandum that accompanied that report.

"It would not be unreasonable to exclude all data on patients from this institution from any future analyses," Bivens wrote.

The ORI report on the Poisson investigation listed only five publications affected by scientific misconduct.

The ORI report did not claim to offer the authoritative list of affected publications. However, another list, compiled by NSABP interim leadership following Fisher's firing, claimed to be complete.

That list, contained in an appendix to an action plan for restructuring the cooperative group, listed 18 papers submitted between 1986 and 1994.

In an interview, Fisher's attorney Charrow said he plans to challenge the exclusion of all St. Luc data regardless of whether it was submitted by Poisson.

"The only person they had any proof against was Dr. Poisson," Charrow said to **The Cancer Letter**. "There is no proof against any other physician at St. Luc who was enrolling patients in NSABP clinical trials."

Dangerous Data?

A review of literature by **The Cancer Letter** found that at least five papers labelled "scientific misconduct" were expressions of opinion by Fisher.

Two of those publications listed Fisher as the only author:

- "The Evolution of Paradigms for the Management of Breast Cancer: A Personal Perspective," Cancer Research, 52(9):2371-2383, 1992. The article appeared under the heading "Perspectives in Cancer Research."
- Fisher's 1992 Steiner Award lecture, published in International Journal of Cancer, 55(2):179-180, 1993.

Also labelled were:

- "On the Underutilization of Breast-Conserving Surgery for the Treatment of Breast Cancer," an editorial by Fisher and Leora Ore, published in the Annals of Oncology, 4:96-98, 1993.
- "New Perspectives on Cancer of the Contralateral Breast: A Marker for Assessing Tamoxifen as a Preventive Agent," an editorial by Fisher and NSABP biostatistician Carol Redmond, JNCI, Sept. 18, 1991.
- "Adjuvant Therapy in Node-Negative Breast Cancer. A Panel Discussion." The discussion between Fisher, William McGuire, Martin Abeloff, John Glick, I. Craig Henderson and C. Kent Osborne was published in Breast Cancer Research and Treatment, 13(2):97-115, 1989.

The only possible explanation for flagging editorials and panel discussions is their reliance on NSABP studies, Charrow said. However, if that criterion is to be applied to Fisher, it should be applied to other authors who cite NSABP studies, he said.

"Followed to its illogical conclusion, a warning flag should be placed on the conclusions of the final document of the 1990 NIH Consensus Development Conference on the Treatment of Early-Stage Breast Cancer," Charrow said.

Drawing heavily on NSABP data that included patients from St. Luc, that conference concluded that breast preservation is the preferable treatment for women with stage I and II disease.

Differences Between Databases

In at least one case, a tag was placed on a paper from a study that clearly fell outside the time frame of the Poisson investigation, which, according to ORI documents, found that falsified records at St. Luc existed since 1976.

The study traced long-term mortality among patients who received radiation treatment prior to 1975:

"Cause-Specific Mortality in Long-term Survivors of Breast Cancer Who Participated in Trials of Radiotherapy," John Cuzick, et al., Journal of Clinical Oncology, 12(3):447-453, March 1994. The paper, which lists Fisher among the authors, was

flagged both in Medline and Cancerlit.

A review of Medline and Cancerlit shows that publications were not flagged in a coordinated fashion.

Medline did not flag at least three papers that listed Poisson among authors and included fraudulent data. Two of those papers were cited in the ORI report on Poisson.

The papers are:

- Fisher et al., "Eight-Year Results of a Randomized Clinical Trial Comparing Total Mastectomy and Lumpectomy With or Without Irradiation in the Treatment of Breast Cancer," New England Journal of Medicine, 320(13): 822-828, March 30, 1989.
- Fisher et al., "A Randomized Clinical Trial Evaluating Tamoxifen in the Treatment of Patients with Node-Negative Breast Cancer who Have Estrogen-Receptor-Positive Tumors," NEJM, 320(8):479-484, Feb. 23, 1989.

Another paper that escaped the flag in Medline despite the fact that it listed Poisson as an author and contained St. Luc data was:

- Fisher et al., "Two Months of Doxorubicin-Cyclophosphomide With and Without Interval Reintroduction Therapy Compared With Six Months of Cyclophosphamide, Methotrexate, and Fluorouracil in Positive-node Breast Cancer Patients With Tamoxifen-Nonresponsive Tumors: Results from the NSABP Project B-15," Journal of Clinical Oncology , 8(9):1483-1496, 1990.

All three papers were flagged in Cancerlit.

In fact, the parameters of Cancerlit appeared to have been altered to allow for tagging of an expanded number of Fisher's articles, Charrow said.

Typically, Cancerlit citations are arranged in reverse chronological order, and at this time, the database runs back from 1994 to 1988. However, in the case of Bernard Fisher, the bottom boundary drops back to 1979, Charrow said.

For those extra nine years, a Cancerlit user sees nothing but flagged papers by Fisher. A literature check for entries on Poisson found three papers written before 1988.

An Unpopular Action

The flagging of Fisher's papers has met with sharp criticism from clinical cancer researchers nationwide.

- "This is the computer equivalent of the air brush that removes people from the reviewing stand at the May Day parade," said O. Ross McIntyre, former chairman of the Cancer and Leukemia Group B, invoking imagery from the Moscow Trials of the 1930's.
- "I think this is the most unfortunate approach and a disservice to clinical trials," said Norman Wolmark, chairman of NSABP. "I hope NCI will remedy this transgression."
- "It seems unbelievably extreme to me," said Charles Coltman, chairman of the Southwest Oncology Group, who said he was surprised by NCI's use of the tag line beyond papers that reported primary clinical trials.

"I don't know where you stop when you begin doing that," Coltman said. "I am not surprised that Bernie and his attorneys are outraged by this approach."

- "It's gratuitous, vindictive, inaccurate, and it contributes nothing to our understanding of cancer," Emil J Freireich, professor of oncology and hematology at M.D. Anderson Cancer Center said.

Freireich said he was stunned to find the tag on Fisher's "Evolution of Paradigms" paper.

"That paper is a brilliant, innovative, original formulation of the modern paradigm of breast cancer, and it has been confirmed over and over again," he said. "There is no controversy about the science here. This is personal."

- "This is the blunderbuss approach to government," said James Holland, professor at the Mt. Sinai School of Medicine.

"Bernard Fisher is one of the towering figures in medical science of the last half of the 20th century. To paste him as if he were a villain is a complete disregard of the scientific process.

"I react to this with dismay that the NLM has been dragged in to the fiasco that I believe represents the conduct of NCI in this attempt to sort out the problems that faced NSABP."

- "First of all, I think the data from all NSABP trials has been reanalyzed, both with the fraudulent data included and excluded, and Dr. Fisher eloquently presented this analysis at the May 1994 meeting of the American Society of Clinical Oncology," said John Glick, director of the Univ. of Pennsylvania Cancer Center and ASCO president-elect.

"While those results have not been published, the oral presentation showed that none of the NSABP scientific conclusions were altered by the removal of fraudulent data. Therefore, the NSABP contribution to scientific advancement of breast cancer research

remains valid.

"Obviously, we are awaiting the republication of NSABP papers in peer reviewed journals, and I think those papers will convince the public that none of the NSABP results have significantly changed," Glick said.

Asked whether he believes that the publication in which he appears as a coauthor warranted a "scientific misconduct" tag, Glick said:

"That was a panel discussion, and there is nothing in that paper that would warrant any warning about scientific misconduct whatsoever."

NCI Of Canada Plans Review Of Breast Screening Study

The National Cancer Institute of Canada will investigate whether randomization procedures were compromised in the National Breast Screening Study, an official said last week.

David Beatty, executive director of the NCIC, which coordinated the study, said the review was prompted by a scientific article in the Feb. 15 issue of the journal Cancer. The article, by an NCI biostatistician, said a flaw in the NBSS may have biased the study against finding a benefit from mammography screening for women under age 50 (**The Cancer Letter**, Feb. 10).

"Questions continue to surface and it is our feeling that it is owed to those who have undertaken the trial and participated in the trial, and those who are basing health policy decisions on the trial to put this issue to rest," Beatty said to **The Cancer Letter**.

NCIC will appoint an independent panel to review the study's procedures. "We are initiating a review of the randomization process and procedures," Beatty said. "Our approach is to, first, have an arms-length evaluation of the randomization records."

The NBSS investigators conducted a review of the randomization records themselves and published the results, Beatty said. "We don't expect any problem in this area," he said. "Depending on what is observed, we may make further decisions."

The review is expected to be completed this year.

NCIC was responsible for the administration of the NBSS, but the study was funded by a consortium of organizations, including the Canadian Cancer Society, research and volunteer organizations, and Canadian government agencies. The study, which was initiated in the 1970s, cost a total of $17 million Canadian.

Reinventing NCI

Bishop: Scientists Need Seat On NCI Executive Committee

The NCI Executive Committee, the highest decisionmaking body in the Institute, should be broadened to include senior scientists, the co-chairman of a working group reviewing the Institute's intramural research program said last week.

Michael Bishop, co-chairman of the National Cancer Advisory Board Ad Hoc Working Group on NCI Intramural Programs, said he received letters from intramural scientists complaining of their lack of involvement in decisionmaking.

"The senior scientists find the executive leadership very remote," Bishop said to the working group last week. "It is a recurrent theme in some of the correspondence I have received."

Bishop and other working group members said they were concerned whether the Institute's structure allows younger scientists to explore their ideas and gives senior scientists enough involvement in the decisions that affect the direction of the science.

"People Feel Decisionmakers Are Remote"

NCI Deputy Director Edward Sondik said he met with senior scientists last week to discuss the accessibility of the Institute's leadership and the idea of broadening the Executive Committee. "I think people feel, especially in times like this, that the decisionmakers are remote," Sondik said to the working group. "We need to make an effort to communicate."

The NCI Executive Committee consists of the NCI director, deputy director, administrative officer, division directors, and the director of the Frederick Cancer Research and Development Center. The committee meets weekly.

"Why are there no senior scientists on the Executive Committee?" Bishop asked. "These folks are seeking regular contact."

Sondik said the committee is small for sake of efficiently. "There is a need to carry out the enormous quantity of the Institute's business," he said. NCI staff members occasionally are invited to give a presentation to the committee, he said.

However, the membership of the committee could be expanded, since the committee is not mandated by law, Sondik said.

There are other methods by which NCI's top executives get information and ideas from staff

members, Sondik said. The director holds a weekly scientific seminar, to which NCI scientists and extramural scientists are invited. In addition, the division directors are expected to have regular contact with senior scientists, and become their advocates at Executive Committee meetings.

Alan Rabson, director of the Div. of Cancer Biology, Diagnosis and Centers, said his senior staff work with laboratory chiefs and junior staff. "If there is any discontent, [the junior staff members] usually call me and I work it out with the lab chief," he said to the working group.

"Is there an opportunity for bottom-up initiatives?" Bishop asked.

"I do have some examples," Sondik said.

"The issue is not examples, but how is it built into the process?" said working group member David Baltimore. "Or is it left to, 'Call Al'?"

In the extramural program, initiatives come from individual scientists working through the peer review system, Sondik said. "For the intramural program, it is built into the way the lab and branch chiefs run their programs," he said.

Initiatives proposed by staff members can work their way through the hierarchy to the Executive Committee, Sondik said. "It is the responsibility of the division director to represent [the staff]," he said.

The Need for "A Sense of Ownership"

Bishop said that from the working group's first meeting, he was surprised by the lack of senior scientists on the Executive Committee. At Univ. of California, San Francisco, scientists serve on similar committees and are involved in running the university, he said.

"It is not a question of advocacy, but of scientific judgment," Bishop said. "I'm not demeaning the scientific judgment of the [division] directors, but there is a larger pool of expertise to draw on.

"It is one thing to feel [the science] will be properly advocated; it is another to feel a sense of ownership in the Institute," he said.

Sondik said he did not think the senior scientists were far from the decisionmaking. "When you say it, it sounds as if the science is more remote than I see it," he said. "I have the sense that the division directors are very close to those people."

Downsizing Not Strategically Planned

The downsizing of NCI staff levels over the past two years is expected to continue and is not being strategically planned, Sondik said to the working group. The Administration's buyout program of offering incentives for employees to leave did not allow for planning.

"This is not based on a detailed analysis of programs," Sondik said. "Particularly if you hold out the green and see who responds."

However, NCI has formed several committees to help deal with the reductions, he said. An intramural committee is led by Claude Klee, chief of the Laboratory of Biochemistry. The extramural committee is led by Brian Kimes, director of the Centers, Training and Resources Program.

The working group has been given a copy a document Sondik called the "Hard Times Committee report." **The Cancer Letter** has filed a Freedom of Information Act request for this document and other documents being reviewed by the working group.

In addition, NIH as required NCI to submit a streamlining plan by April, Sondik said.

The buyout program was a small part of NCI's staff reductions, said Philip Amoruso, director of the Office of Administrative Management. About 300 NCI staff members were eligible for the buyouts and 3 percent to 4 percent took the offers, he said. More difficult has been the freeze on hiring and promotions, he said.

"There are selected areas where we want to make reductions, particularly in administration of grants and contracts," Amoruso said.

"Is there any discussion of the science?" Bishop asked.

"The division directors have been taking cognizance of this and [work with] lab and branch chiefs to adjust the science accordingly," Amoruso said.

Rabson said NCI hoped to get advice from the working group. "To do anything now, for example, to eliminate a program, would be the wrong thing to do while we are awaiting a new director," he said.

NCI Gets 16% Of NIH AIDS Funds

NCI receives 16 percent of all NIH funding for AIDS research, William Paul, director of the NIH Office of AIDS Research, said to the working group. Most of the money funds intramural research.

In FY95, NCI received $218 million for AIDS research. The President's budget for FY96 calls for $225 million. Over the past decade, increases for AIDS have exceeded increases for cancer research.

Working group member Leon Rosenberg asked

what was driving the increase for AIDS research. "Has there been a strategic plan to convert the NCI to the 'National AIDS Institute'?" he asked.

"There has been a mandate for NIH to do AIDS research," Sondik said. "I don't see it as a concerted drive from within NCI to make NCI the 'AIDS Institute.'"

Some observers have said the increases for AIDS research are hurting cancer research, Bishop noted.

Prior to the recognition of AIDS as a public health crisis, NCI scientists were working on related research, Sondik said.

"The question is, at what point does [AIDS research] become not supportive [of cancer research]," Sondik said. "I have heard division directors say it is cutting into the cancer effort."

FDA Advisors OK Dox-SL For Conditional Approval

An FDA advisory group last week recommended conditional marketing approval for pegalated liposomal doxorubicin HCl (trade name Dox-SL) for the treatment of AIDS-related Kaposi's sarcoma in patients who have failed prior systemic chemotherapy.

If adopted by FDA, the conditional approval would require the sponsor, Liposome Technologies Inc., of Menlo Park, CA, to conduct additional studies to substantiate the drug's safety and efficacy after marketing has begun.

The FDA Oncologic Drugs Advisory Committee made the recommendation Feb. 14 following a four-hour discussion of the company's data, which committee members described as disorganized and incomplete.

In other action, ODAC recommended marketing approval for goserelin acetate implant (trade name Zoladex) for palliative treatment of advanced breast cancer in pre- and perimenopausal women.

FDA: Six Patients Benefited In Study

Dox-SL consists of doxorubicin encapsulated in a tiny sphere which contains polyethylene glycol on its surface.

In a study with 383 patients, LTI retrospectively identified 77 patients who had disease progression on prior combination chemotherapy, or who were treatment-intolerant. Forty-five patients had received anthracycline. The partial response rate was 34 percent after a median of 65 days of therapy based on observation of specific lesions.

For observations based on standard diagnostic criteria for Kaposi's, the partial response rate was 43 percent after a median of 113 days of Dox-SL therapy.

Half of the patients experienced reversible neutropenia, and a small percentage experienced a cardiac event attributed to the drug.

In his analysis, FDA reviewer Anthony Murgo found only six patients for whom there was a clear evidence of benefit. "It was difficult if not impossible to make assessments of clinical benefits of the drug on pain, edema, quality of life outside a randomized, controlled trial," Murgo said to the committee.

Among those who received prior anthracycline therapy, 52.2 percent experienced partial response as indicated by specific lesions, and 30 percent showed the same progression when compared to standard criteria, according to Murgo's analysis.

Among those who did not receive anthracycline, the partial response rates were 42.1 percent as indicated by lesions and 21. 4 percent when compared to standard criteria, Murgo said.

"The committee was in consensus that the data to date do not demonstrate the product's effectiveness sufficiently to qualify for normal approval at this time," FDA said in a statement following the meeting.

ODAC voted 10-0 to recommend that the company consider submitting an application for approval of Dox-SL under FDA's accelerated approval mechanism.

Advanced Breast Cancer Palliation

Following the Dox-SL discussion, ODAC quickly granted full marketing recommendation for Zoladex for palliation of advanced breast cancer, particularly in women with positive hormonal status.

In one study of 37 patients, comparing the drug to oophrectomy, 26 percent of the patients treated with Zoladex experienced either a complete or partial response, as compared to 47 percent of those who underwent surgery.

In another study of 124 patients, 22 percent of those treated with Zoladex experienced complete or partial response, as compared to 13 percent of the oophrectomy patients.

Panel member Sandra Swain said the studies were neither large enough nor long enough in duration for differences in survival to be statistically meaningful.

The meeting marked the first time that an ad hoc patient representative was allowed to participate in each drug discussion (**The Cancer Letter**, Feb. 17).